



RHODE ISLAND MEDICAL JOURNAL

December 1991

Volume 74, Number 12



Gallstone Disease



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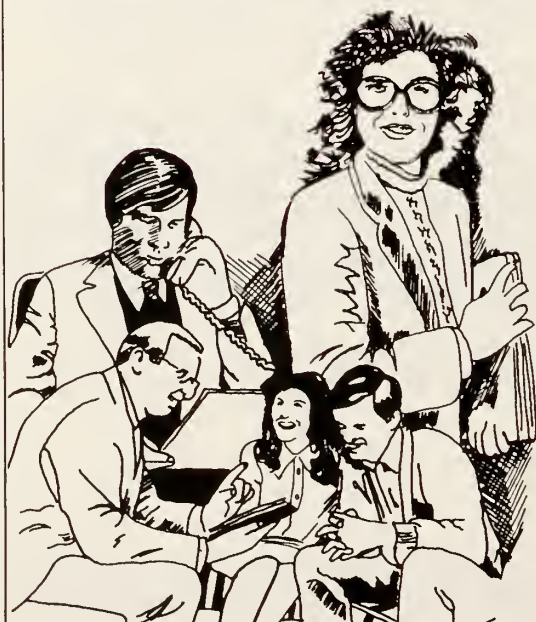
Cover: A woodcut by Albrecht Dürer (1471-1528) of Nuremberg graphically portraying melancholia, a pervasive emotional state believed at that time to be the result of an excess of black bile (ie, melancholia). Galen had proposed that temperament was the balance between the four internal humours (blood, phlegm, yellow bile and black bile) resulting variously in the optimistic, the sluggish, the choleric and the melancholic personalities.

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A Right Upper Quadrant Revolution

"When will gallstones make the first division of the research league?", wondered Franz Inglefinger, Editor of the *New England Journal of Medicine*, in 1968. In 1991, stones may be dissolved, crushed, exploded, blended or extracted by chemical, electrical, percutaneous, or endoscopic technics. As this ever-expanding panoply of therapeutic possibilities has emerged, the gold standard of surgical cholecystectomy may be supplanted by newer laparoscopic technics with a smaller incision, less operating time and hospital stay, and perhaps lower morbidity.

Basic science advances have triggered development of each of these exciting new technologies. The fundamental abnormalities leading to secretion of abnormal bile remain uncertain. Nonetheless, the rapid proliferation of knowledge about cholesterol and bile salt homeostasis has permitted a true revolution in the clinical approach to the gallbladder and gallstone disease.

The research agenda for the future is a full one. The pathogenesis of cholelithiasis remains to be elucidated. Development of pharmaceutical agents to prevent gallstone formation is in its infancy. Clinical trials are needed to assess the appropriate role for competing therapies

to treat the diseased gallbladder. Each current, non-surgical treatment of gallstones is beset with problems of safety, efficacy, or recurrence risk that limit current application to a small percentage of afflicted individuals. Unanswered questions abound, but revolutionary progress is being made.

The current issue of the *Journal* presents the reader with three views on these newer therapeutic modalities. The first of these contributions addresses the questions: What symptoms indicate gallstone disease? Should the silent stone be left in peace? And, what are the high risk groups with silent stones? The second paper, by Schaberg, reviews the author's extensive experience with laparoscopic cholecystectomy. The third paper, by Malik, considers the problems, and advances, in the endoscopic management of stones in the bile ducts.

Edward R. Feller, MD

The Varied Uses of Gallstones

Today's physician rarely considers the gall bladder, and its ducts, as anything more than a simple reservoir and conducting system for bile. The biliary

apparatus is acknowledged to be the frequent site of inflammation and calculus formation, but certainly it is not regarded as a precious, romantic or exotic object. The human gall bladder today is resected in large numbers, its tissue given a cursory histologic examination, and it is then discarded along with the stones it frequently harbors. Neither the banality of its anatomic structure nor the commonness of its diseases convey any hint of the exaltation which the gall bladder—and its pathologic products—have inspired in other cultures.

For centuries apothecaries have prized the gall stones of oxen for their alleged worth in the therapy of epilepsy. The yellow stones are dried, pulverized and the resulting powder then instilled into the nostrils of the patient. No double-blind field trials have been conducted to judge whether the merit of gall stone dust extends any further than its placebo effect, but in some parts of the world the powder is still found on the shelves of drug dispensers.

Oxen gall stones are largely composed of cholesterol and for centuries they have been powdered and mixed with oil to form yellow ochre, a pigment employed by many graphic artists.

The belief in the restorative and analgesic powers of gall

bladder tissue makes them objects of occasional value. On October 22, 1991, in the Bay Ridge section of New York City, a Korean-American merchant had been murdered. The victim specialized in the export of certain animal parts to be used by overseas herbalists and other healers. Police conjectured that the killer had removed an undetermined number of bear gall bladders which were known to have been stored in the merchant's freezer. Black bear gall bladder, noted the police, is considered a powerful aphrodisiac in Asia; it is said, also, to possess special pain-relieving attributes. "Grizzly bear gall bladders," they declared, are hard to come by because fewer than 1,000 grizzlies are left in the continental US." The Fish and Wild Life Service further disclosed that a bear gall bladder can bring about \$10,000 on the black market and one bear gall bladder is known to have been sold for \$45,000. (Human gall bladder removal, performed for obviously humanitarian reasons, generates a much more modest return.)

Gall, a word of Teutonic origin, originally meant the color yellow but, because of its taste, came to mean bitterness as well. The gall bladder was regarded by ancients as the internal organ which tempers one's character in the direction of unbridled anger, asperity and bitterness of spirit. Bile, a word of Latin derivation and one of the four fundamental humours, was sometimes called choler and was held responsible for ill-temper and impudence. Indeed, the biliary personality possessed a stereotyped character well known in European literature. One learned, scientific text at the end of the last century, declared the following: "A person who is of a

biliary nature should live sparingly and take plenty of exercise. He should avoid fat and rich food, butter, pastry and sauces, and should drink no beer or wine—unless it be some very light French wine or Moselle. He should keep his bowels regular and even loose, taking every morning a dose of sulphate in a glass of hot water. A course at Carlsbad, Vichy or Contrexeville may be helpful." They just don't write textbooks like that anymore.

Stanley M. Aronson, MD

The Language of Epidemiology (VI): Prevalence

An incidence rate (of disease X) tells us the speed with which new cases of X enter the community of the living. (And similarly, the mortality rate of X tells us the exiting velocity from the living community.) We need yet another measure to describe, at a given instant, what proportion of the population is made up of persons with a particular disease or other attribute. The attribute can be anything which is objectively measurable whether it be gender, a demographic characteristic, a biologic variation, or a frank disease. The attribute can be enduring (eg, blood type) or fleeting (eg, acute respiratory infection). This cross-sectional measure is called *prevalence*.

A prevalence, usually expressed as a percentage, provides us with an instantaneous profile, a cross-section, of the studied community in terms of the attribute being considered (eg, disease X.) By its nature, prevalence is a dichotomous

expression, neatly dividing the world under observation into those with the disease (or other attribute) and those without the disease (or other attribute). No other factors enter into the equation of prevalence. For example, if we read that 2% of the population has an acute respiratory infection (ARI), at the designated time of measurement, we interpret this as a fulfillment of the equation below. Note that the number with ARI plus the number without ARI make up the total population under study:

$$\frac{(\text{No. with ARI})}{(\text{No. with ARI}) + (\text{No. without ARI})} \times 100 = \text{prevalence}$$

Prevalence, an essentially stable statistic, reveals only that which exists at the very moment of inquiry. Prevalence nevertheless represents a dynamic balance between the numbers of cases materializing and those resolving, the chronicity of the disease studied, and the threshold of sensitivity above which we diagnose the disease. The weight of these other forces cannot however be deduced from the prevalence statistic alone. In a steady state, therefore, prevalence equals newly introduced cases minus cures and deaths, tempered overall by the accuracy of our diagnostic skills, and divided by the total population.

Is there any relationship between prevalence (of disease X) and the incidence rate of disease X? Prevalence seems to represent a simple fraction while rate is a more complex synthesis of movement from the population of the healthy to the population of the sick, and is therefore an index of transitional speed. Can there then be a crude algebraic correlation between the two

measurements? In general, when the prevalence is not substantial, there is:

Prevalence (of X) =

Incidence rate (of X) x Mean duration (of X)

Or, expressing it somewhat differently, mean duration of disease X approximately equals its prevalence divided by its incidence rate. The brevity of a disease such as ARI, therefore, results in a yearly incidence rate which is extremely high (almost equalling the population number), but a prevalence typically less than two percent. Most humans have at least one ARI episode per year but at any one time (on average) fewer than 2% will be burdened by an ARI.

Assuming now that the incidence rate of X remains unchanged, what circumstances might impel the prevalence of X to rise or fall? There are four mechanisms which may cause this:

1. When disease X becomes more chronic, perhaps because of the introduction of new therapies (such as insulin) which do not cure but nevertheless permit indefinite survival with the disease. Thus, at any one time, there are more living cases of X even though the rate of new cases of X, per unit time, is unchanged. If, on the other hand, a rapid cure is now devised and made readily available, the incidence rate of disease X may still remain unaltered but the prevalence will diminish in proportion to the degree of access to this new therapy.

2. If more comprehensive clinical screening procedures are adopted (eg, mobile vans with chest X-ray equipment for the detection of pulmonary tuberculosis) the ascertainment of disease X increases as hidden cases in the community are now revealed.

3. If newer, more sensitive tests are instituted which identify the disease in its earlier, perhaps preclinical, phase (eg, mammography, exfoliative cytology tests, etc.) the duration of illness X is necessarily made longer by identifying the disease earlier in its natural history, therefore causing the prevalence to rise despite an unchanged incidence rate.

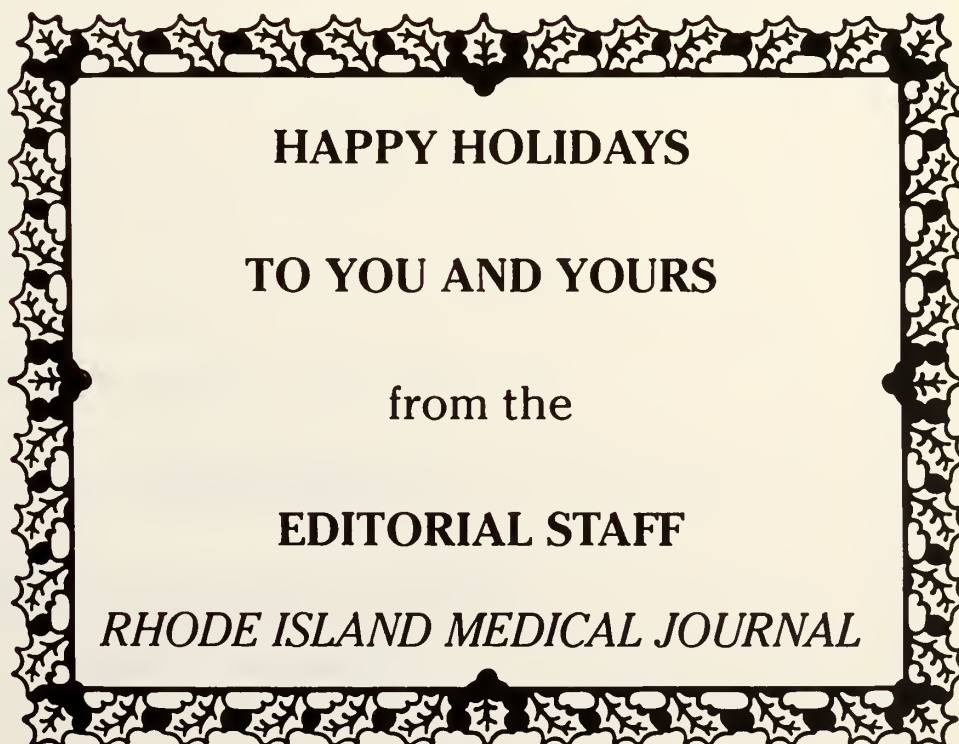
4. If there is a selective migration of people with disease X into or out of the community under study (eg, there might be a facility for the treatment of tuberculosis or AIDS in a particular city which may attract, from elsewhere, those already diagnosed with the particular disease. Thus the local incidence rate is unaltered but the local prevalence will rise.).

The ascertainment rate (the degree of success in identifying

the frank cases of disease X in the community) is influenced necessarily by societal attitudes. If the disease were viewed socially as neutral, no unusual ascertainment problems will arise; but if the disease carries some social stigma (eg, sexually transmitted infections) ascertainment is inevitably impeded.

The prevalence of disease X in general, is a less informative statistic than the incidence rate of disease X. Prevalence tells us only the proportion of the population with disease X and not the numeric risk (probability) of acquiring disease X during a given time interval. Prevalence has limited utility in telling us the fraction burdened with the disease, the immediate realities, but it offers no predictive information; it fails to inform us of tomorrow's threats.

Stanley M. Aronson, MD



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The Natural and Unnatural History of Gallstones

Edward R. Feller, MD

. . . 15 million Americans have or will develop gallstones.

As recently as 10 years ago, cholecystectomy was the unrivalled management choice for cholelithiasis. Recent advances have altered therapeutic possibilities for gallstone disease. Appropriate use of proliferating treatment options requires an understanding of the natural history of biliary stones.

The prevalence of gallstones is uncertain. Post-mortem population studies in the United States and Western Europe indicate that perhaps 10% of men and 20% of women have gallstones. Necroscopy subjects may not be representative of living populations. A recent stratified random sample of 1,896 British adults¹ indicates that, as expected, prevalence rises with age; at 60-69 years of age, 22.4% of women and 11.5% of men had gallstones or had undergone a cholecystectomy. Extrapolation of these rates to the United States population suggests that 15 million Americans have or will develop gallstones.

Edward R. Feller, MD, is Clinical Associate Professor of Medicine at Brown University, Providence, Rhode Island.

What symptoms indicate gallstone disease?

Evidence indicates that individuals with gallstones and recent biliary-type pain are at great risk for recurrent symptoms. Recent data from the National Cooperative Gallstone Study indicate that about 70% of patients who had pain prior to the study developed recurrent episodes within two years compared to about 13% who had been previously asymptomatic.²

Though most patients with typical biliary symptoms merit therapy, usually cholecystectomy, there is surprisingly little consensus regarding which clinical manifestations indicate a gallbladder source. Symptoms from gallstones are non-specific with considerable overlap in complaints from patients without biliary disease. Classic symptoms, including colicky pain, fatty food intolerance, flatulence, and nausea have poor predictive value for a positive diagnosis of cholelithiasis. More importantly, these symptoms correlate poorly with prediction for symptom relief from cholecystectomy. Gallbladder origin is supported by radiation of pain to the back, a steady not

colicky quality, duration between 1 and 24 hours, and onset more than an hour after meals.³ Nonetheless, symptoms due to cholelithiasis are non-specific, and clinical assessment is insensitive.

Patients with "typical" biliary complaints and evidence of gallstones on roentgenographic imaging studies pose no diagnostic dilemmas. What should the approach be to the patient with chronic, intermittent, right upper quadrant pain in the absence of gallstones on either ultrasonography or cholecystography and normal biliary scintigraphy? Such individuals may have a variety of disorders including intestinal gas, irritable bowel syndrome, acid peptic disease, as well as small stones or a disorder of biliary motility. Identification of patients with chronic acalculous cholecystitis related to chronic inflammation resulting from poor gallbladder motility would permit differentiation of a sub-group who would be expected to benefit from surgery. Quantitative evaluation of gallbladder motility using cholecystokinin biliary scanning to detect delayed emptying has been used to identify patients with biliary dyskinesia who

might benefit from cholecystectomy.⁴ Others⁵ have reported contrary results, suggesting that abnormal gallbladder emptying does not correlate with presence or absence of gallbladder pathology or outcome after cholecystectomy. Ongoing controlled trials may resolve these conflicting, inconclusive results.

The asymptomatic gallstone: Should the silent stone be left in peace?

A Tale of Two Patients

Patient A is a 50-year-old woman with three episodes of sharp right upper quadrant pain lasting an hour and awakening her from sleep. Ultrasound examination demonstrates multiple gallstones.

Patient B is a 50-year-old woman who has had no medical complaints until she developed abdominal discomfort after hitting a steering wheel in a car accident. Ultrasound examination demonstrates multiple gallstones.

For patient A, cholecystectomy is the gold standard for definitive treatment to avoid frequent recurrent attacks of acute cholecystitis and its potential complications (cholangitis, choledocholithiasis, biliary pancreatitis). Cholecystectomy cures cholelithiasis in 100% of cases with an operative mortality as low as 0.1% and quite uncommon sequelae, such as retained common bile duct stones. However, for Patient B, the silent gallstone commonly remains so. In 1909, William Osler stated, in his *Principles and Practice of Medicine*, "most gallstones caused no symptoms".

Accumulating evidence indicates that incidentally discovered, silent gallstones uncommonly cause subsequent clinical problems. In a large screen-

ing study of men with asymptomatic gallstones, Gracie and Ransohoff reported a 10% cumulative incidence of subsequent biliary symptoms within 5 years and an 18% cumulative incidence at 10 years.⁶ Urgent surgery was rare. These findings have been confirmed by others. Only 15 of 139 patients with co-incident stones discovered on ultrasonography developed biliary pain within 5 years in another follow-up study.⁷ Of these patients, 6 of 139 eventually required cholecystectomy for symptoms. Thus, the natural history of asymptomatic gallstones in unoperated patients appears to be quite benign. However, some groups with asymptomatic stones have a different, more complicated natural history.

High Risk Groups with Silent Stones

The calcified or "porcelain" gallbladder

Patients with a significant risk of developing carcinoma of the gallbladder, such as individuals with a calcified or "porcelain" gallbladder, may benefit from prophylactic cholecystectomy. As many as 50% of these patients will have gallbladder carcinoma at surgery.

Sickle Cell Disease

Patients with sickle cell anemia and gallstones may have symptoms impossible to distinguish from those of a sickle cell crisis and merit definitive therapy. In sickle cell disease, increased bilirubin production occurs due to hemolysis with formation of pigmented calcium bilirubinate stones. The clinical manifestations of gallstones and sickle cell crisis may be indistinguishable: abdominal pain, nausea and vomiting, fever, leukocytosis, and jaundice.

Emergency surgery in these patients is fraught with potential complications. Prophylactic cholecystectomy is recommended for stones.

Diabetes Mellitus

Management of asymptomatic stones in diabetics continues to be controversial. Gallstones in diabetics were formerly thought to be associated with a markedly increased incidence of acute cholecystitis and gangrene of the gallbladder. Mortality of biliary surgery in diabetics was deemed prohibitive. Recent studies have suggested that diabetics do not have a higher incidence of complications than non-diabetics, nor is life expectancy or quality of life increased by prophylactic cholecystectomy.⁸ A poorer prognosis in diabetics with cholelithiasis results from more frequent associated, co-morbid illness, especially vascular and renal disease, rather than any intrinsic increased risk.

Post-Laparotomy

In patients undergoing laparotomy for other indications, incidentally discovered gallstones may behave less benignly than silent stones discovered in other clinical settings. In one large series, 50% of patients with incidental gallstones left *in situ* at laparotomy developed biliary symptoms within six months of surgery.⁹ This puzzling finding has been confirmed by others in a variety of surgical settings.¹⁰ Post-operative fasting or vagotomy may increase gallbladder stasis and distention. Other contributing factors may be dehydration of narcotic medication affecting gallbladder motility. What remains unclear is whether high-risk groups should be screened pre-operatively with ultrasonogra-

phy, and what are appropriate indications for incidental cholecystectomy at laparotomy.¹¹

Table 1. Silent Stones – High Risk Groups

Porcelain gallbladder
Sickle cell anemia
? Diabetes mellitus
Morbid obesity
Post-laparotomy
Children

Morbid Obesity

Patients with morbid obesity have frequent and virulent gallbladder disease with as many as 70% having symptoms.¹²

Marked weight loss, either by diet or surgery, further increases the risk of symptoms from gallstones. Coincidental cholecystectomy is recommended at the time of surgery for morbid obesity if stones are discovered.

Children

Gallstones are rare in the pediatric age group and are usually secondary to an underlying illness including congenital hemolytic anemia, ileal disease, or metabolic defect. Most children with stones develop symptoms, and prophylactic surgery is frequently appropriate.

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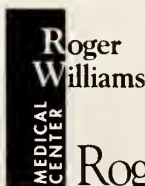
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Laparoscopic Cholecystectomy

Frank J. Schaberg, Jr, MD

Although many surgeons initially considered laparoscopic cholecystectomy a stunt, they were driven by public demand, as much as by scientific data, to learn and perform the procedure.

"Be not the first by whom the new are tried, nor yet the last to lay the old aside." –Alexander Pope, an essay on criticism (1711)

Since first described by Langenbuch in 1882,¹ the safety and efficacy of laparotomy and cholecystectomy in the treatment of symptomatic gallstones has been well established. Because of the perceived morbidity of the procedure, alternatives have been investigated and "marketed" in recent years. None of these have caught the professional or public imagination as has laparoscopic cholecystectomy.

Unlike any other medical procedure in recent memory, laparoscopic cholecystectomy has gone from its first description in a human, by Dubois in France in 1987,² to becoming standard practice in only 3 years.

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Although many surgeons initially considered laparoscopic cholecystectomy a stunt, they were driven by public demand, as much as by scientific data, to learn and perform the procedure. It is of particular note that the initial evaluation and early teaching of this procedure was centered not in major university teaching hospitals, but primarily in the hands of surgeons in private practice.³ This reversal of the "usual order of things" is one of the many unique features of the evolution of this operation.

The rapidity with which surgeons have trained in laparoscopic cholecystectomy has been frightening. The number of centers performing the procedure and the number of courses given nationwide has grown exponentially. The enthusiasm for the procedure has spawned, in this short period of time, at least two journals devoted purely to endoscopic surgery, and at least two new surgical societies. The entrepreneurial fever to "cash in" on this demand and offer courses where instructors have barely learned the procedure

themselves has provoked real concern. Within the surgical community, the issues of training, credentialing and monitoring of safety and quality have become paramount.^{4,5}

In spite of these concerns, there is little doubt that the procedure can be mastered by most competent surgeons, and that with a reasonable degree of care and judgment it is both safe and effective.

Indications

The indications for laparoscopic cholecystectomy are the same as for open cholecystectomy. Patients with documented cholelithiasis and signs or symptoms attributable to their diseased gallbladder are the prime candidates. An occasional patient with asymp-

ABBREVIATIONS USED:

ERCP: endoscopic retrograde cholangio-pancreatography
MHRI: Memorial Hospital of Rhode Island

matic gallstones (patients on immunosuppression and possibly some diabetics), gallbladder polyps, or patients with biliary symptoms without stones may be considered for laparoscopic cholecystectomy.

It has been tempting for some to consider the ease with which most patients tolerate laparoscopic cholecystectomy as an excuse to extend the indications for its prophylactic use. This philosophy is to be condemned not only because of its fallacious reasoning, *a priori*, but also because experience has indicated that there are significant perioperative complications. Some patients who appear to be ideal candidates for laparoscopic cholecystectomy will still require laparotomy because of technical factors discovered at the time of their laparoscopy.

Contraindications

There are few absolute contraindications to laparoscopic cholecystectomy (Table 1). The procedure requires general anesthesia, and any medical condition precluding safe general anesthesia precludes cholecystectomy. Patients with clinically evident peritonitis, acute suppurative cholangitis, severe coagulopathy which cannot be adequately medically reversed, biliary fistula or suspected carcinoma should not undergo this procedure. Relative contraindications include previous upper abdominal surgery, cirrhosis, untreated common bile duct calculi, pregnancy and massive obesity (Table 2).

The Procedure

The only significant difference between laparoscopic cholecystectomy and open cholecystectomy is the absence of an abdominal incision. What is accomplished anatomically is the

Table 1. Contraindications to laparoscopic cholecystectomy

- 1) Peritonitis
- 2) Cholangitis
- 3) Uncorrected coagulopathy
- 4) Biliary fistula
- 5) Suspected malignancy
- 6) Medical condition precluding general anesthesia

same. In both procedures the entire gallbladder is removed and the biliary ductal system visualized by intraoperative cholangiography. The procedure is carried out under general anesthesia. A nasogastric tube and urinary catheter are placed to facilitate visualization by decompressing these organs and protecting them from possible injury.

Both are removed at the conclusion of the procedure. Perioperative antibiotics are administered as with any cholecystectomy. Pneumoperitoneum is created using carbon dioxide, and a camera is inserted through a 1 centimeter operative trochar placed in the periumbilical incision. Following insertion of the camera, the procedure is carried out under direct vision utilizing television screens so that the entire operating team can watch. Operating and retracting trochars are inserted and the gallbladder is placed on traction. The patient

is placed in reverse Trendelenburg position, and the cystic duct and artery are dissected. The inferior edge of the cystic duct is usually easily visualized and serves as an anatomic landmark to prevent injury to vital structures in the porta hepatis. When the cystic duct and artery are clearly delineated, a cholangiogram is carried out. The duct and artery are then secured with clips or ligated, and divided. The gallbladder is dissected from the liver bed with either electrocautery or laser for cutting and hemostasis, and withdrawn through either the umbilical or epigastric trochars. If the gallbladder contains a stone or stones too large to fit through the 1 centimeter incision, they can usually be crushed prior to delivery, or if necessary the incision may be slightly enlarged. Prior to closure, the operative site is examined for hemostasis. If necessary, a drain may be left as in open cholecystectomy.

Table 2. Relative contraindications to Laparoscopic Cholecystectomy

- 1) Previous upper abdominal surgery
- 2) Untreated common duct calculi
- 3) Cirrhosis
- 4) Obesity
- 5) Pregnancy
- 6) Pacemaker

Table 3. Representative Results of Laparoscopic Cholecystectomy

Author	Number	% Converted	% Morbidity	% Bile Duct Injury
Soper ¹²	300	1.3	1	.3
Spaw ⁸	500	1.8	1	0
Shirmer ⁶	152	8.5	4	.7
Zucker ⁷	100	5	2	1
*MHRI	75	5	1	0

*The current series.

Results

Although this procedure has been in clinical use worldwide for less than 3 years, there have already been numerous reports of series ranging from 50 to several hundred cases 6-8 (Table 3). In Rhode Island, the first laparoscopic cholecystectomy was carried out April 30, 1990 at Rhode Island Hospital.⁹ Within the next month, several were carried out at Memorial Hospital of Rhode Island and at Roger Williams General Hospital, and subsequently virtually every hospital has adopted this technique. It has become the standard operation for removal of the gallbladder. Although the cumulative results of the cases carried out in Rhode Island have not been tabulated,* the results from the early experience at Memorial Hospital are representative of what is being accomplished locally and serve as

a good comparison with published reports.

Between June of 1990 and June of 1991, 130 laparoscopic cholecystectomies were carried out at Memorial Hospital of Rhode Island. Complete data are available for the first 75. Of these there were 69 female patients and 6 males with an average of 46.1 years (15-82). Of these first 75, 71 were successfully completed laparoscopically, 4 (5.3%) were converted to open cholecystectomy. Sixty-seven patients remained in the hospital 24 hours or less. Two remained 48 hours, 1 patient 72 hours, and 1 patient 5 days. The prolonged stays were all related to ileus, which resolved without any specific treatment. There were no deaths and no major operative complications. Virtually all patients returned to full activities within 1 week of the time of their operation.

The 4 patients "converted" to open cholecystectomy were all for findings of severe inflammatory disease involving the gallbladder, portohepatis, and often adjacent colon and omentum making safe visualization of the anatomy impossible (Table 4). Clinical signs such as pain, fever, abdominal tenderness or the presence of a palpable mass did not correlate with the need for open cholecystectomy. Two of our 4 patients were purely elective with relatively mild chronic symptoms. Among the patients successfully completed laparoscopically, several had acute cholecystitis. The patients who were converted to open cholecystectomy all had uncomplicated postoperative recovery consistent with that operation. None were found at exploration to have had major complications related to the attempted laparoscopic dissection.

Operative cholangiography was attempted in 17 of the first 75 patients and completed in 15. Since that time, cholangiography has been carried out in almost all the laparoscopic cholecystectomies.

Discussion

The demonstration that laparoscopic guided cholecystectomy can accomplish the same thing as open cholecystectomy with minimum morbidity has revolutionized this operation. The marked diminution in operative pain, significant decrease in length of stay, and minimum time out of work are not only a vast improvement from the patient's point of view, but have dramatic cost-saving implications.

Although the incidence of major complications has been acceptably low, a note of caution is being sounded by many

Table 4. Reasons to "convert" to open cholecystectomy

- 1) Uncontrollable bleeding
- 2) Known or suspected bile duct injury
- 3) Visceral injury
- 4) Inability to clearly delineate anatomy
- 5) Unexpected finding of cancer
- 6) Common duct stone not likely to be amenable to endoscopic resolution

interested in the development of safe laparoscopic surgery.^{10,11} There have been major complications including common bile duct transection and ligation, and injuries to the intestine requiring laparotomy and surgical repair. There have been postoperative fatalities. The recognition of these complications is a sobering thought to surgeons interested in the development of these technics.

There has been considerable speculation in the literature about the cause of intraoperative injuries.¹⁰ It is still not clear whether there is an inherently higher risk of common bile duct injury in laparoscopic cholecystectomy than in open cholecystectomy. The overall reported incidence of bile duct injury to date in laparoscopic surgery is 0.6%. The accepted figure in open cholecystectomy is 0.2%. There is some concern that the "two-dimensional" view offered by the camera is responsible for these problems, or that the use of laser or cautery result in thermal injuries to the duct or intestine with delayed necrosis and perforation. The major concern has been whether these types of injuries are more likely to occur in one's early experience and be the result of "the learning curve," and thereby avoidable by proper training and supervision. The final answer to these questions is not in.

The only significant difference between laparoscopic surgery and open cholecystectomy is the absence of an abdominal incision.

There is no doubt in the surgical community that it is absolutely essential that anyone at-

tempting laparoscopic cholecystectomy be a trained, experienced surgeon well-versed in the nuances of biliary tract surgery and biliary anatomy. The concept that the lack of an abdominal incision opens up this type of surgery to other medical subspecialists who are accustomed to endoscopic procedures is ludicrous.

As this procedure has become standardized, hospitals have developed their own credentialing procedures. It is clear that this is not a procedure that can be learned even by someone experienced in biliary surgery, by reading about the technic or simply watching a video tape. Specific training in the safe accomplishment of laparoscopy as well as the specific technic of laparoscopic cholecystectomy is necessary utilizing classroom instruction, animal models and experience in the observation and proctored performance of this surgery in humans.

At Memorial Hospital in Rhode Island we have utilized a team approach that has been very successful. We allow only surgeons who have been fully trained in the procedure to perform it, and insist that the assistant surgeon be similarly trained. Using this technic, we have had remarkable success with minimal complication, and found that this "shared experience" has been invaluable to all involved.

The simultaneous development of endoscopic and radiographic procedures for the management of common bile duct stones has contributed significantly broadening the applicability of laparoscopic cholecystectomy. In the patient in whom the preoperative workup by history, laboratory data or imaging has indicated significant likelihood of common duct cal-

culi, preoperative endoscopic stone retrieval has been successfully carried out. The suspicion of a common duct stone is no longer an indication of open cholecystectomy. The patient at high risk for such stones should undergo ERCP preoperatively. If this can be accomplished, laparoscopic cholecystectomy remains the operation of choice.

A small number of patients will be found to have "silent" common duct stones by cholangiography at the time of their surgery. Although initially there was some controversy about whether this was an indication to convert to open cholecystectomy and common duct exploration, it is now believed that most patients are best served by completing the operation laparoscopically, and addressing the stones postoperatively by other minimally invasive means. Technological advances allowing for laparoscopic removal of common duct stones through operating choleoscopes and laser lithotripsy are being developed, and in the relatively near future will become standard practice in most hospitals.

The suspicion of a common duct stone is no longer an indication for open cholecystectomy.

The initial reaction of many surgeons to the idea of removing the gallbladder through a laparoscope was scorn. It was common to hear them say that they would never allow themselves or someone in their family to undergo this procedure, that it violated all the principles that they had learned and practiced through their careers, and that it was worthy of any proper

surgeon's condemnation. In the short time that laparoscopic cholecystectomy has been available, it has become abundantly clear that none of these are true. "One of the greatest pains to human nature is the pain of a new idea" (W Bazehot, Physics and Politics 1869).

Almost daily the surgical literature (and simultaneously the *New York Times*, National Public Radio, *The Providence Journal* and the Donahue show) is reporting new "stunts" accomplished laparoscopically. Already in relatively common use is laparoscopic herniorrhaphy and appendectomy. There have been numerous reports of highly selective vagotomy, nephrectomy, hysterectomy and retroperitoneal node biopsy carried out endoscopically. The European literature has described colon resection and anastomosis. Although these procedures are unlikely to become widespread in the short period of time it took for laparoscopic cholecystectomy to "catch on," the future of such technics is limited essentially only by the imagination and technological advance of the instrument makers and the surgical community.

"The old order changeth yielding place to new." (*Tennyson, Idylls of the King, 1885*)

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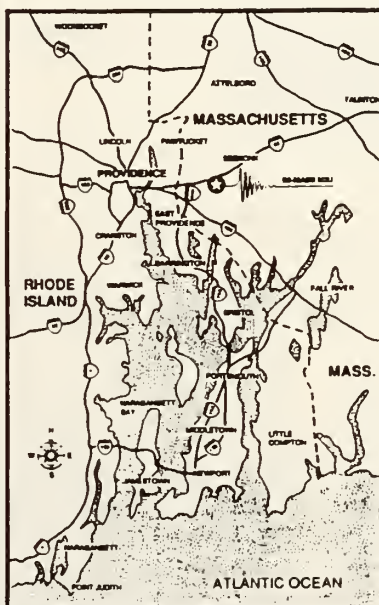
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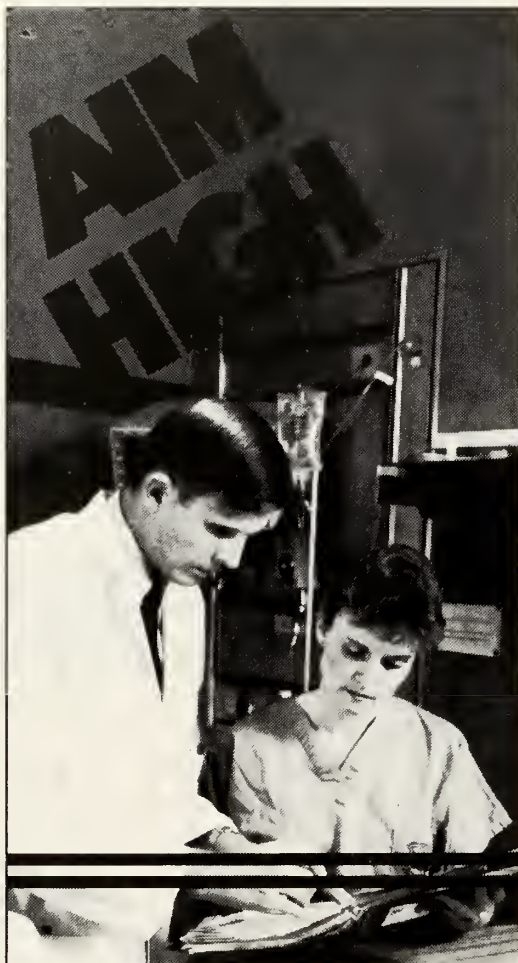


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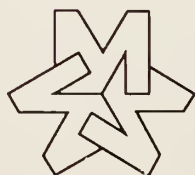
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Amer Malik, MD

About 15% of patients with gallstones also have stones in the common bile duct.

Endoscopic technics have revolutionized the management of biliary duct stones. Duodenoscopy followed by cannulation of the ampulla of Vater and injection of contrast material into the pancreatic and biliary ducts is widely used in the diagnosis of a wide range of pancreatic and biliary problems. An application of this technic using endoscopic sphincterotomy to cut ampullary muscle fibers and allow endoscopic removal of common duct stones has also become widely utilized. In addition, once a stone in the duct has been documented, a variety of technics exist to remove, crush, or dissolve calculi. With the popularity of laparoscopic cholecystectomy increasing, the demand for endoscopic management of biliary stones is expected to rise as a pre-laparoscopic procedure.

Clinical Significance of Biliary Stones

About 15% of patients with

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gallstones also have stones in the common bile duct. In most cases, these stones have migrated from the gallbladder, though primary common duct stones can exist. Although many stones are detected via intraoperative cholangiography at the time of cholecystectomy, retained stones do occur in about 5 to 10% of cases.¹ Technical factors may prevent detection of stones at cholecystectomy including inflammation obscuring the common bile duct, inability to properly turn patients during surgery to obtain optimal films, as well as small stones hidden behind folds in intrahepatic ducts. T-tube cholangiography will detect some of these stones; however, some will be missed and may present with symptoms stemming primarily from obstruction of the bile duct. Acutely, the patient may present with biliary colic, jaundice, cholangitis, or pancreatitis. Chronic biliary obstruction can lead to cirrhosis; and rarely, hepatic abscesses may form.

The natural history of asymptomatic stones is not well known. Although bile duct stones can remain asymptomatic for months to years, they probably cause symptoms more

frequently than gallbladder stones. Because of potential illness, it is advisable to remove any stones present in the biliary tract whether they are symptomatic or not.

ERCP and Sphincterotomy-Technic

The duodenal ampulla is located about 2 inches from the pylorus. The common bile duct exits through this ampulla of Vater sharing a common channel at the distal tip with the pancreatic duct over 80% of the time.² A sphincter is present at the ampulla composed of smooth muscle fibers.

A lateral viewing endoscope is used to image the biliary and pancreatic ducts. The ampulla of Vater is viewed 'en face' when the endoscope is in the duodenum. A polyethylene catheter is then inserted into the ampulla and contrast injected thus imaging the pancreatic and biliary ducts with fluoroscopy. Once

ABBREVIATIONS USED:

CBD: common bile duct
ERCP: endoscopic retrograde cholangio-pancreatography
ERS: endoscopic retrograde sphincterotomy

stone(s) are confirmed, another catheter with a 20-30mm exposed wire ('sphincterotome') is inserted into the biliary duct. This wire is connected to a diathermy unit. The wire is 'bowed' by pulling on the wire proximally and electrodiathermy applied allowing the ampullary sphincter to be incised (ERS). The electrodiathermy is applied in a controlled, stepwise fashion. This is *extremely* important, otherwise a too rapid incision ('zipper cut') may lead to complications. The length of the cut is 5-15 mm depending on the size of the stone and certain landmarks which indicate the limit to which the ampulla can be cut safely. A catheter with an inflatable balloon is then inserted, inflated to 8-14mm distal to the stone. The balloon catheter is then dragged out along with the stone, in a sweeping manner. Alternatively, a basket with 4-6 wire loops which can be opened like an umbrella can be used to trap and drag the stone out. Mechanical lithotripsy baskets are used in a similar fashion but they are stronger and can crush the stone. The major limitation to sphincterotomy usually is the size of the stone. Anatomical alteration of the upper GI tract can also make it more difficult, for example a person with Billroth II gastroduodenal anastomosis. The main contraindications to sphincterotomy are significant coagulation defects and stones greater than 2.5 cm in diameter.

If stones cannot be removed, drainage from the bile duct can be obtained temporarily by either leaving an indwelling stent or nasobiliary tube, thus avoiding the potential complication of biliary obstruction and its sequelae. These are placed by inserting a long wire through the diagnostic cannula, withdrawing

the cannula, and leaving the wire in place in the bile duct. The stent (by aid of a long 'pusher' tube) or nasobiliary tube is then advanced over the wire until it is in place. The wire and pusher tube is then withdrawn. The position is confirmed with fluoroscopy.

Because of potential illness, it is advisable to remove any stones present in the biliary tract whether they are symptomatic or not.

ERCP and sphincterotomy are relatively safe procedures. The overall complication rate with ERCP alone is reported to be around 2% with a mortality rate around 0.1%.^{3,4} The most common complication is pancreatitis (usually mild, occasionally severe).

There have now been more than 12,000 endoscopic sphincterotomies reported. There is good concordance in most series with respect to sphincterotomy complications. The overall complication rate with sphincterotomy is in the region of 7%, primarily pancreatitis, bleeding, and perforation, with a mortality rate under 1%.⁵

Comparison of ERCP with other modalities

If stones in the common bile

duct or gallbladder are suspected, the initial imaging study is usually a right upper quadrant ultrasound. Ultrasound is very good at detecting gallstones in the gallbladder but only detects CBD stones in 13-55% of cases.⁶ Dilated ducts, as indirect evidence of choledocholithiasis, can also be missed in as many as 36% of cases.⁶ The results from CT scanning are similar. Percutaneous cholangiography although comparable to ERCP in detecting bile duct stones does not lend itself so readily to therapeutic options. Moreover, apart from the discomfort of inserting the needle into the liver, percutaneous cholangiography is seldom successful in imaging *nondilated* bile ducts.

Acute cholangitis

Acute cholangitis is a closed space infection due to obstruction of biliary outflow most commonly caused by a stone. Therefore, antibiotic treatment is not definitive. Its mortality has decreased from nearly 100% to between 9-40% with the combination of antibiotics and biliary drainage.⁷ If the cholangitis is unimproved after 24-48 hours with antibiotics, some form of drainage is required urgently. Traditionally, surgery has been used. Leese et al⁸ studied records of 82 patients with de-

Table 1. Endoscopic Therapy for Bile Duct Stones

INDICATIONS
Uncomplicated bile duct stones
Acute Cholangitis
Acute gallstone pancreatitis
Post-cholecystectomy
High risk/elderly patients with gallbladder in situ
Pre- or post-laparoscopic cholecystectomy

scending cholangitis, comparing surgical intervention with ERS. The surgical 30 day mortality rate of 24% was similar to prior reports in the literature (8-33%) but was much higher when compared to the 4.7% rate in patients with ERS ($p < 0.002$). As expected, patients undergoing endoscopy were older with more risk factors. This would favor endoscopic decompression as the procedure of choice in acute cholangitis.

Of course, if the patient improves with antibiotic therapy alone, the bile duct will still need to be imaged and decompressed. Any stones present in the bile duct will need to be removed either surgically, or with ERS if the patient is elderly or not a surgical candidate. If the gallbladder has been removed previously, bile duct stones can be removed endoscopically.

Gallstone Pancreatitis

At least 50% of cases of acute pancreatitis are caused by gallstones.⁹ A stone migrating into the common channel can obstruct it leading to bile reflux into the pancreatic duct. This bile reflux in turn can initiate the activation of trypsinogen and the subsequent autodigestion is postulated to cause pancreatitis.¹⁰ However, the concern in trying to relieve the obstruction surgically or endoscopically has always been the possibility of increased morbidity and mortality in a patient with an inflamed pancreas.

Ultrasound is very good at detecting gallstones in the gallbladder but only detects CBD stones in 13-55% of cases.

Despite these concerns, cannulation of the pancreato-

biliary ductular system has been shown to carry low risk. This was shown most definitely in a randomized prospective trial.¹¹ 121 patients were randomized to either urgent ERCP/ERS (within 72 hours) or conventional treatment. In patients with severe gallstone pancreatitis, 54% had complications in the conventional arm vs 18% in the ERCP/ERS group ($p = 0.035$). 3/24 people died in the conventional group. There was no mortality in the ERCP/ERS group. No difference between groups was noticed in patients with mild pancreatitis. It is worth noting that the operators were highly skilled, and endoscopic intervention in this setting should be performed by endoscopists with similar capabilities.

Postcholecystectomy syndrome

Postcholecystectomy syndrome is a general term for discomfort to pain following cholecystectomy. In many cases, the cause is simply dyspepsia. Choledocholithiasis, pancreatitis, biliary stricture, etc. need to be considered. Liver function tests and ultrasound may be indicated. ERCP is usually the most helpful test however and is indicated in anyone with severe abdominal symptoms or 'obstructive pattern' liver function. It is expected that about half the patients with 'post cholecystectomy syndrome' will have an abnormal ERCP.

Biliary colic

Biliary colic is a descriptive term generated from the patient's history. Both cystic duct obstruction and distal common bile duct obstruction by stones cause biliary colic. Symptoms alone cannot differentiate the two. In 5% of the cases stones are present only in

the bile duct¹¹ and if the ultrasound does not show any stones in the gallbladder, an ERCP should be obtained.

Sphincterotomy is the procedure of choice for bile duct stones in all patients with significant risk factors for surgery, whether or not the gallbladder is present.

Sphincterotomy in patients with biliary stones and intact gallbladder

Sphincterotomy in patients with biliary stones and an intact gallbladder is generally performed only if there are significant risk factors to the procedure or if the patient is elderly. Large numbers of patients have now been reported with long follow up. Significant complications occur in about 10-15%,¹² mainly cholecystitis. Sphincterotomy is the procedure of choice for bile duct stones in all patients with significant risk factors for surgery, whether or not the gallbladder is present.

Laparoscopic cholecystectomy

Laparoscopic cholecystectomy has gained tremendous popularity. How can ERCP help patients undergoing laparoscopic cholecystectomy? Studies examining this topic have not been done as yet. If stones are detected in the bile duct during laparoscopic cholecystectomy, an ERCP is recommended post-procedure to remove them. In those patients with a high suspicion of common bile duct stones prior to surgery, such as jaundice, cholestasis, bile duct dilatation, or stones seen on imaging studies, such as ultrasound or CT, ERCP should be performed pre-op-

eratively. In those patients with a high suspicion of bile duct stone, technical failure of visualization of the biliary tree by ERCP should encourage an open cholecystectomy rather than a laparoscopic procedure. This sequence would avoid the scenario of laparoscopic cholecystectomy with unsuccessful cholangiogram followed by unsuccessful ERCP followed by conventional open common bile duct exploration. Controlled trials are needed to determine whether ERCP followed by laparoscopic cholecystectomy is superior to open cholecystectomy with common bile duct exploration as the primary treatment for stones found in both the gallbladder and common bile duct in the same patient.

Methods of Stone Removal by ERCP

Spontaneous passage of common duct stones occurs in as many as 50% of cases after sphincterotomy has opened the ductal orifice. If a stone does not pass spontaneously, stones may be extracted under direct endoscopic control via a balloon extractor or basket extraction. Crush baskets are also available which may be placed endoscopically in the bile duct, thus allowing disintegration of stones which pass spontaneously. It is also possible to pass a nasobiliary cannula endoscopically into a duct to instill solvent, such as mono-octanoic acid, for stone dissolution. Prototype models for ultrasound or laser dissolution of common duct stones have been introduced for use with ERCP. In the high-risk patient with a very large stone which is unable to be removed endoscopically, it has been possible to place stents in the bile duct which act as a wick, thus pre-

venting jaundice, cholangitis, or pancreatitis. In the specific cases, the stone may be left *in situ*.

Conclusion

ERCP and ERS are valuable technics that have enhanced greatly the management of bile duct stones. Stone-induced disease is thus more accessible to non-operative intervention. Large series have shown ERCP and ERS to be safe and effective in comparison to other treatment modalities. Any stone detected in the bile duct should be considered for removal due to its high potential to produce acute and chronic problems. Recent studies have confirmed the utility and safety of ERCP in acute situations, such as cholangitis and pancreatitis, to diagnose and potentially treat choledocholithiasis as an inciting factor. Minimally invasive laparoscopic surgery will necessitate more interaction between the surgeon and the biliary endoscopist, although the role for ERCP and ERS in this setting is still being defined.

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Assisted Reproductive Technics for the Treatment of Male Factor Infertility

Mark Sigman, MD

... approximately 15% of couples attempting their first pregnancy meet with failure.

Over the last decade, increased emphasis has been placed on the achievement of parenthood. Unfortunately, approximately 15% of couples attempting their first pregnancy meet with failure. These patients are defined as primarily infertile if they have been unable to achieve a pregnancy after one year of unprotected intercourse. In approximately one third of cases, significant pathology is found in the man alone and in another 20%, a male factor is contributory to the couple's infertility. Thus, in roughly 50% of infertile couples, the male factor is at least in part responsible for the failure to conceive. It has often been recommended that clinical evaluation of the male partner be delayed until after one year of unprotected intercourse has passed. However, with many couples attempting conception in their 30s, the ini-

tial screening of the man should be considered whenever the patient presents with a chief complaint of infertility. Unduly prolonged, unprotected intercourse should not be advocated before a work-up of the man is instituted. This initial evaluation should be rapid, non-invasive and cost effective.

As the basis of any type of male evaluation for infertility should be the standard technics for evaluating medical problems in general: a complete history

and physical examination as well as the analysis of all pertinent laboratory tests. This initial evaluation should be directed at determining if a male factor is involved in the couple's fertility. These studies should try to identify a specific cause for the couple's infertility. If a particular etiology is identified (ie, infection, varicocele, etc.) treatment should be specific for that entity.

Approximately 25% of patients will be classified as hav-

ABBREVIATIONS USED:

AMP: adenosine monophosphate
ART: assisted reproductive technics
DIPS: direct intraperitoneal insemination
FRED: fallopian replacement of eggs with delayed intraperitoneal insemination
GIFT: gamete intrafallopian transfer
hCG: human chorionic gonadotropin
ICI: intracervical insemination

IFV-ET: in vitro fertilization-embryo transfer
IUI: intra-uterine insemination
POST: peritoneal ovum and sperm transfer
PROST: pronuclear stage tubal transfer
TEST: tubal embryo stage transfer
TET: tubal embryo transfer
THI: therapeutic husband insemination
ZIFT: zygote intrafallopian transfer

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ing idiopathic male infertility in whom no specific etiology for an abnormal semen analysis can be found. For these patients, as well as for those in whom no specific etiology for an abnormal semen analysis persists after specific therapy, assisted reproductive technics (ART) are indicated. These are technics to improve conception rates by improving the ability of sperm to reach and fertilize ova and result in pregnancies. It must be emphasized that these technics should not take the place of specific treatment directed at improving spermatogenesis. It has been demonstrated that even if a couple proceeds with assisted reproductive technics, conception rates may be improved if underlying abnormalities in the male are corrected prior to the institution of these technics. Thus, it is critical that both the male and the female be evaluated prior to the institution of therapy.

... in roughly 50% of infertile couples, the male factor is at least in part responsible for the failure to conceive.

Unfortunately, many abbreviations have been used in this field, making it difficult to differentiate between individual procedures (Table 1). All procedures involve manipulation of sperm. The sperm may then be placed into the female, as is the case with therapeutic husband insemination (THI). Alternately, eggs may be collected from the female and both sperm and egg may be placed into the female, as is the situation with gamete intrafallopian transfer (GIFT). Lastly, both sperm and egg may be combined in a test tube allow-

ing for in vitro fertilization to occur (IVF-ET).

Semen Processing

All semen processing technics attempt to concentrate a fertile population of sperm. Seminal plasma is removed with all of these technics, while others also select motile sperm and remove leukocytes and non-motile sperm. Various technics are used to accomplish this, ranging from simple sperm washing to various methods of swim-ups, sedimentation, and more complicated Percoll gradient centrifugations (Figure 1). With the use of these technics, the percent of motile sperm in a specimen may be increased. Recent reports suggest that the *in vitro* addition of various compounds, such as pentoxifylline, may allow for improved motility and fertilizing capacity in suboptimal specimens.

Intrauterine Insemination

Intrauterine insemination is commonly employed in the treatment of both male and female factor infertility. This pro-

cedure bypasses the cervical mucus allowing for a higher concentration of sperm to reach the uterus, and hopefully ascend the female reproductive tract. This technic has been used to treat cases of cervical factor infertility as well as male factor infertility, unexplained infertility and immunologic infertility. While intrauterine insemination has been used for male factor infertility for many years, because of differences between studies and the poor design of most studies, it has been very difficult to draw conclusions as to its role in this patient population. Kerin's report, which demonstrated a 21% pregnancy rate per cycle in 34 patients undergoing washed sperm intrauterine insemination with non-stimulated menstrual cycles, resulted in renewed interest in this technic. No pregnancies occurred during intercourse cycles. Not all investigators have found differences between IUI cycles and intercourse cycles.

Recently, ovarian hyperstimulation has been used to induce the women to develop

Table 1. Assisted Reproductive Techniques listed in increasing order of complexity

In Vivo Fertilization	[• Vaginal/Cervical Insemination (ICI)	Sperm Manipulation
		• Intrauterine Insemination (IUI)	
		• Direct Intraperitoneal Insemination (DIPSI)	
In Vitro Fertilization	[• Fallopian Replacement of Eggs with Delayed Intraperitoneal Insemination (FREDD)	Sperm & Ova Manipulation
		• Gamete Intrafallopian Transfer (GIFT)	
		• Peritoneal Ovum and Sperm Transfer (POST)	
		• In Vitro Fertilization and Embryo Transfer (IVF-ET)	
		• Tubal Embryo Transfer (TET, PROST, ZIFT)	
		• Micromanipulation	

more than one egg per cycle. Pregnancy rates of 7-19% per cycle as compared with 0-2.2% pregnancy rates in non-stimulated cycles have been reported in studies combining IUI and hyperstimulation. Thus, in male factor couples consideration should be given to combining IUI with ovarian hyperovulation.

In Vitro Fertilization-Embryo Transfer

IVF-ET was developed for the treatment of female factor infertility, due to obstructed fallopian tubes. With the rapid growth of this modality, many centers are now treating patients with suboptimal semen analyses with this technic. Several steps are involved in IVF-ET. In the first step, hormonal stimulation is used in the woman to induce the development of multiple follicles. Ultrasound is used to monitor the size of developing follicles. The subsequent injection of human chorionic gonadotropin (hCG) causes oocyte maturation (34-36 hours after hCG treatment). Oocytes are harvested from the ova by either laparoscopy or ultrasound guided needle aspiration.

A semen specimen is collected from the man and processed, most commonly using the swim-up technic. Subsequently, the concentration of sperm is adjusted with a goal of approximately 50,000 motile sperm/ml for men with normal semen analyses. In men with suboptimal semen analyses, higher concentrations in the range of 500,000-1,000,000 motile sperm/ml are often used.

In the third phase, insemination is accomplished by mixing the oocytes with the prepared sperm. During a 2-3 day incubation, the sperm and eggs are allowed to fertilize. Following this, the cleaving embryos are placed

Figure 1. Semen Processing. Semen processing techniques which are used for assisted reproductive technologies.

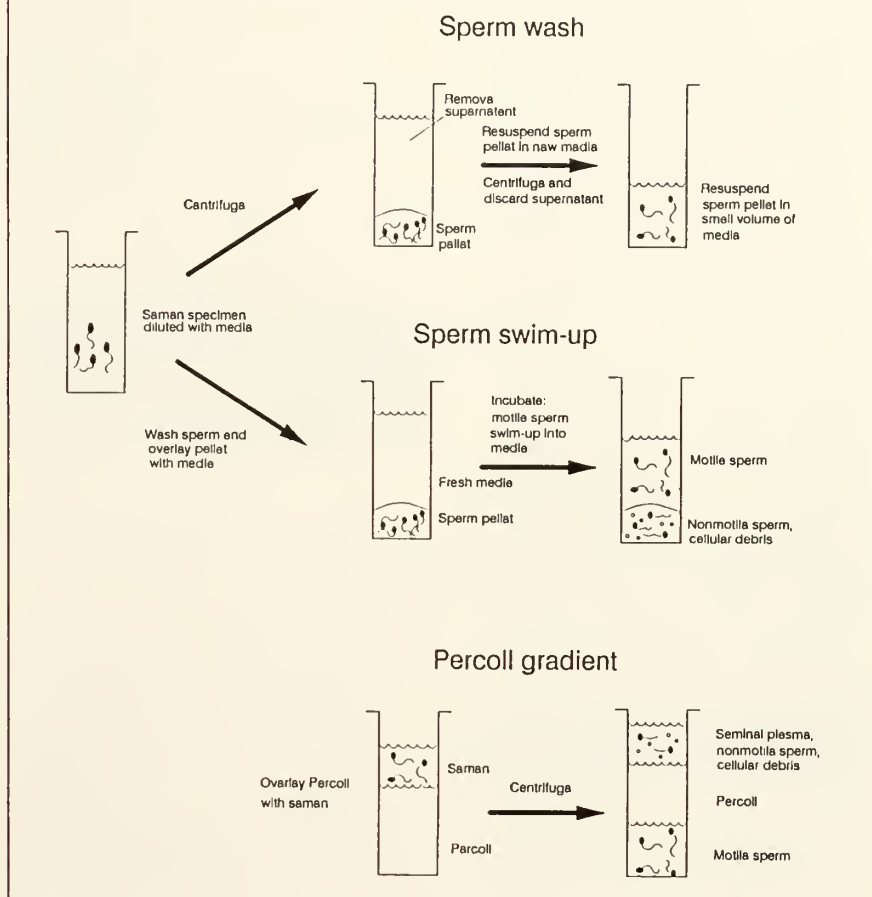
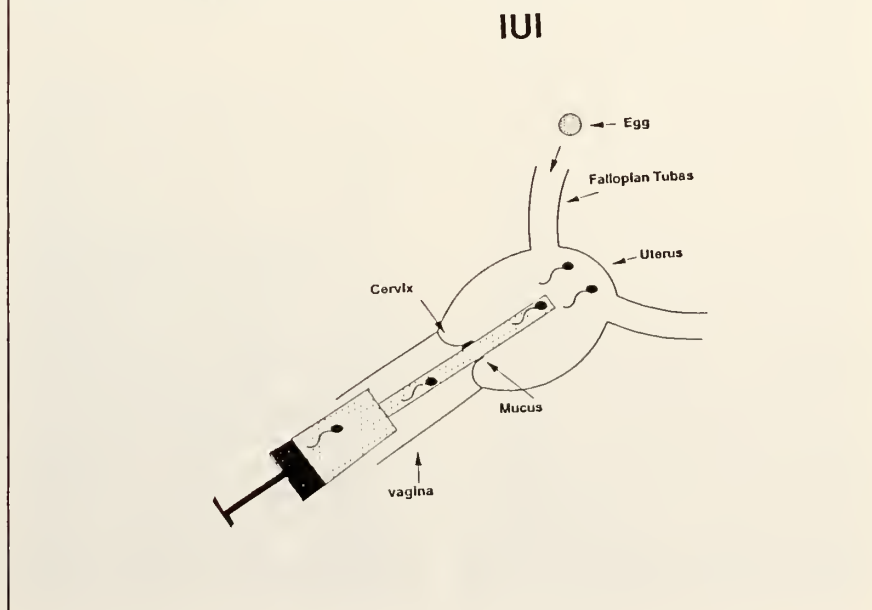


Figure 2. Technic of Intrauterine Insemination. Motile sperm are injected through the cervix into the uterus.



into the uterus (Figure 2). In vitro fertilization will occur in approximately 90% of non-male factor couples. However, implantation and subsequent pregnancy occur in only 20-30% of cases in which embryos are transferred.

The fertilization rate is the percent of ova fertilized *in vitro* divided by the total number of oocytes inseminated. Decreased fertilization rates of 49% have been documented in male factor couples. This occurs despite using higher motile sperm concentrations in male factor couples. Thus, even if the motile sperm concentration is adjusted upwards in male factor patients, the sperm still do not function as well as sperm from non-male factor patients.

The rate of failure of fertilization is the percent of couples undergoing IVF in whom no oocytes fertilize. Failure of fertilization occurs in approximately 10% of non-male couples compared with up to 40% in male factor couples. If no fertilization is obtained in a first IVF cycle, 10-18% of couples will fail to fertilize on a subsequent IVF cycle. Following two failed cycles, most couples will continue to fail to fertilize.

These differences in fertilization rates result in lower pregnancy rates in male factor couples as compared to non-male factor couples. The IVF registry reported that of cycles in which oocytes were retrieved, a 12% biochemical pregnancy rate was obtained in male factor couples as compared with a 16% biochemical pregnancy rate in non-male factor couples. Once a couple has fertilized, however, the male factor couples have as good or better chance of implanting and proceeding to a subsequent pregnancy than non-male factor couples.

It is important to realize that not all biochemical pregnancies proceed to term since approximately 30% of pregnancies abort after IVF. Thus, live birth rates are lower than biochemical pregnancy rates. In IVF cycles in which eggs were retrieved, a 9% live birth rate was reported for male factor couples as compared with an 11% live birth rate in non-male factor couples.

Pregnancy rates of 7-19% per cycle have been reported in studies combining IUI and hyperstimulation.

One must note that these live birth rates and biochemical pregnancy rates are rates per cycle in which oocytes are retrieved. These do not reflect the 10-20% of cycles which do not proceed to ovum recovery.

When examining the effect of semen parameters on IVF, one finds that as sperm concentration in the raw semen specimen drops below 10-20 million/ml, fertilization rates tend to decrease. Similarly, as motilities decrease to below 30-40%, fertilization rates also decrease. A better correlation is found if one examines the motile sperm concentration. The fertilization rate is decreased by approximately 50% when antisperm antibodies are present on the sperm.

Various techniques have been examined in attempts to improve the results of IVF in the male factor population. Unfortunately, it has not been possible to remove antibodies once they are bound to sperm. The addition of other compounds, such as calcium, relaxin, prostaglandins, caffeine, prolactin and dibutyryl cyclic AMP, have all been found to increase sperm motility in vitro. However, these

have not as yet been applied to IVF. Recently, the addition of pentoxifyllin has been found to increase fertilization rates in some cases.

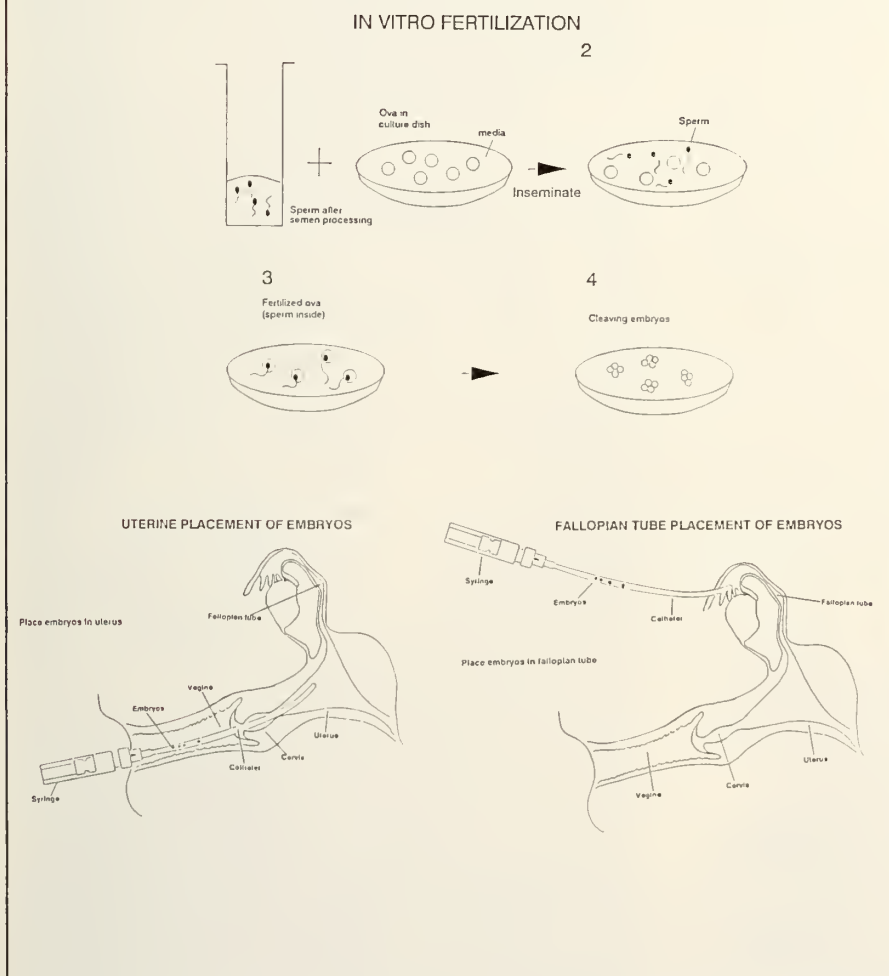
Gamete Intrafallopian Transfer

Since the introduction of IVF, variations of this technique have developed. Gamete intrafallopian transfer (GIFT) is a technique in which ova are retrieved in a manner similar to IVF. However, sperm are mixed together with the ova and injected into the fallopian tube prior to fertilization. Since ova are normally fertilized by sperm in the fallopian tubes, this has the theoretical advantage of allowing fertilization to occur in a more physiologic manner and avoids *in vitro* embryo culturing. A disadvantage is that when couples undergo this procedure, the ability of the husband's sperm to fertilize the wife's oocytes is not determined. This is precisely the step which male factor couples have difficulty with. The results of this procedure in male factor couples has revealed pregnancy rates similar or higher than those found in IVF.

Tubal Transfer Techniques

Another variation of *in vitro* fertilization attempts to combine the benefits of GIFT with the advantages of *in vitro* fertilization. These techniques known by different names: pronuclear stage tubal transfer (PROST), zygote intrafallopian transfer (ZIFT), tubal embryo transfer (TET), tubal embryo stage transfer (TEST), all involve the *in vitro* fertilization of human eggs followed by placement of the early stage embryo back into the fallopian tube. Yovich, et al, reported a 37% pregnancy rate in couples undergoing tubal transfer and a 35.9% pregnancy

Figure 3. Technique of *in vitro* fertilization with uterine placement of embryos. For tubal transfer procedures, the embryos would be placed into the fallopian tubes.



rate in patients undergoing the GIFT procedure. This was compared to a 12.5% pregnancy rate in patients undergoing standard *in vitro* fertilization. While this study was retrospective and uncontrolled, other similar studies have demonstrated similarly high pregnancy rates. A disadvantage of tubal transfer technics is that they generally require a laparotomy or laparoscopy for placement of embryos; whereas uterine placement is an office based, nonanesthetic procedure.

From a review of the available data, it is clear that male factor patients have lower fertilization rates as compared to non-male factor groups. However, once fertilization has taken place in male factor couples, the pregnancy rate is as high or higher than that in non-male factor couples. Live birth rates remain low at approximately 5-10% per stimulated cycle in male factor couples. These rates may increase with tubal transfer technics. However, there remains much room for improvement in

the use of these technics in the treatment of male factor couples.

Micromanipulation

Implantation rates may be increased by tubal transfer technics. However, with male factor patients, fertilization rates remain a problem. In an attempt to increase fertilization rates, various micromanipulation technics have been developed. Since the zona pellucida around the ovum acts as a barrier to fertilization, attempts have been made to alter this structure. Zona drilling involves placing a micro-pipette containing acid Tyrodes against the zona pellucida. The acid solution dissolves a portion of the zona pellucida allowing access to the oolema. Unfortunately, the acid solution damages human eggs and this process has been abandoned.

... approximately 30% of pregnancies abort after IVF.

In a partial zona dissection or zona tearing, a microneedle is used to tear a portion of the zona pellucida. In an initial report, a 68% fertilization rate was obtained in 18 couples undergoing IVF with micromanipulated oocytes as compared with a 47% fertilization rate in non-micromanipulated controls. The zona pellucida is bypassed completely in perivitelline injection. This procedure involves microinjecting 1-5 sperm into the perivitelline space (the space between the zona pellucida and the ovum plasma membrane). Using this procedure on patients who did not have enough motile sperm to proceed with standard *in vitro* fertilization protocols, a clinical pregnancy rate of 19% was reported. The most invasive of all the micromanipulation proce-

dures involves direct injection of one spermatozoa into the ooplasm. An initial study reported 5 of 11 microinjected oocytes proceeded to pronuclear formation; however, no pregnancies were obtained.

While increased fertilization rates are obtained with micromanipulation, polyspermic fertilization may also occur. Using microneedles, excess pronuclei have been removed from polyspermic zygotes. This technic remains experimental since it is not possible to differentiate between male and female pronuclei. Micromanipulation technics combined with DNA analysis have been utilized to determine the sex of the embryos. This technic holds much promise for the early diagnosis of genetic disease.

Summary

Several treatment choices remain for the couple with male factor infertility due to idiopathic male infertility or in couples in which specific therapy has failed. Empiric medical therapy continues as a viable option; however, the physician and patient must understand that the success rates with any of the pharmacological therapies remain suboptimal. In addition, this therapy should only be used for patients with idiopathic male infertility. It is not indicated for other classes of infertile males.

Another option is that of IVF and related technologies. These technics continue to improve and we can expect more specific technics to be developed to optimize fertilization and pregnancy rates in those couples with male factor infertility. At the present time, the pregnancy rates achieved with this technology in male factor couples are less than those in non-male

factor patients. In addition, all of these technics entail considerable expense, often not covered by insurance.

The third alternative for the patient with idiopathic male infertility is that of therapeutic insemination with the husband's sperm. Recent studies combining ovarian hyperstimulation with IUI suggest a clear advantage of this technic over other insemination approaches. As this treatment is significantly less expensive and time-consuming than the prior therapies, it should be considered when choosing therapy. Additional choices the couple with male factor infertility should consider are adoption and therapeutic donor insemination. It is only after careful consideration of all the available options that an appropriate decision can be made. This will vary, depending on the particular clinical characteristics of the couple as well as their social and financial situation.

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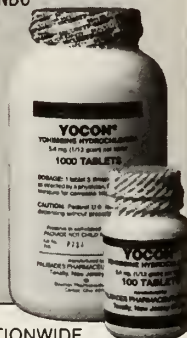
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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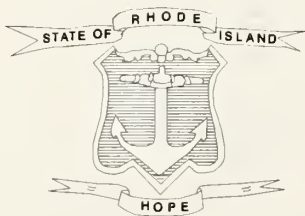
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HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Hospitalizations for Biliary Tract Disease, 1990

During the year ending on September 30, 1990, there were 3,498 discharges from Rhode Island hospitals with a primary or additional diagnosis of biliary tract disease (ICD-9-CM codes 574-576). This number represents 2.5% of the total of 140,095 hospital discharges during that period, placing biliary tract disease among the leading causes of hospitalization in the population. Patients hospitalized for these conditions are of all ages throughout the adult years, with 29% in the 15-44 year age group, 26% in the 45-64 year age group, and 45% age 65 or older. Nearly two-thirds are females, with the female preponderance being largest (84%) among the youngest age group, ie, those age 15-44.

A majority of patients with biliary tract disease fall into a single category, discharges with a primary diagnosis of cholelithiasis, which includes calculus of the gallbladder and calculus of the bile ducts. Virtually everyone of these pa-

tients was treated by cholecystectomy. The age-sex distribution of this group follows that of all patients with biliary tract disease, except that the proportion of elderly among patients with surgical intervention is lower (34%).

Discharge rates for cholelithiasis in Rhode Island mirror those reported for the United States and the Northeast region* during calendar year 1989 (Figure 1). Rhode Island's slightly

lower rate may be due in part to the exclusion of Rhode Island residents discharged from out-of-state hospitals, for whom current data are not available. Comparison of Rhode Island and national rates by age and sex shows that local discharge rates for the middle-aged and elderly are lower by approximately 15% than national rates. Similarly, the rate for females in Rhode Island falls below the national rate (Figure 2).

Figure 1. Rate of Hospital Discharge with Principal Diagnosis of Cholelithiasis, United States, Northeast Region, and Rhode Island, 1989-90.

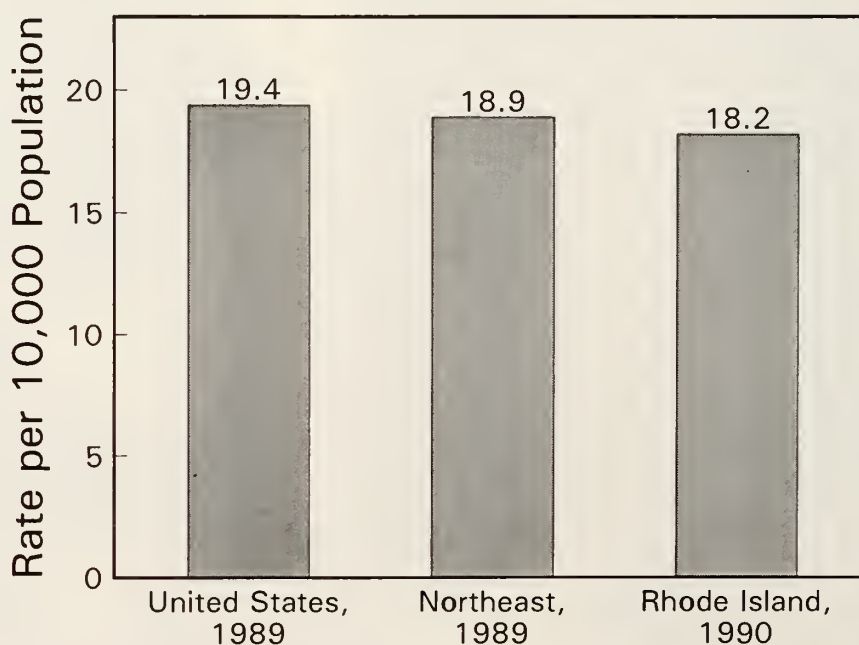
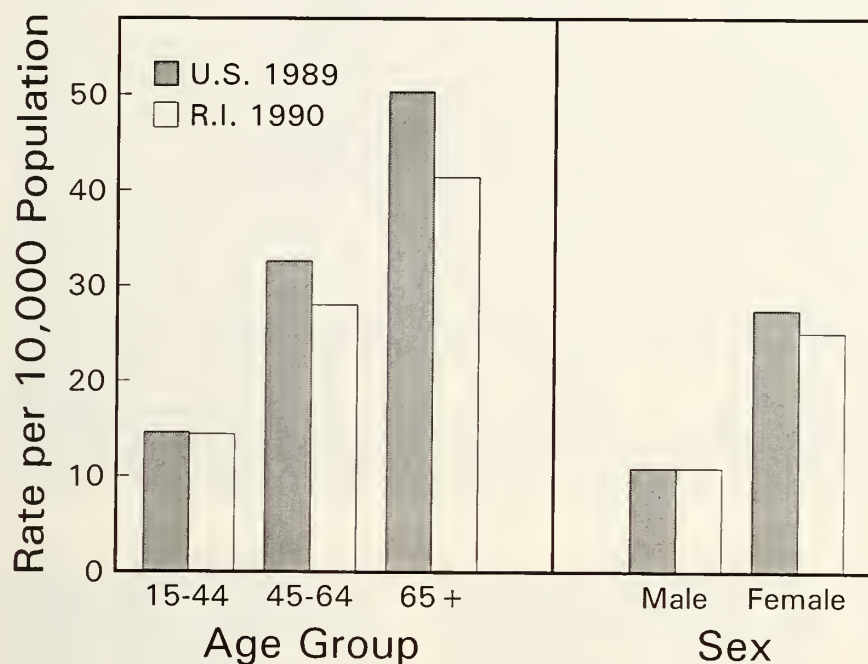


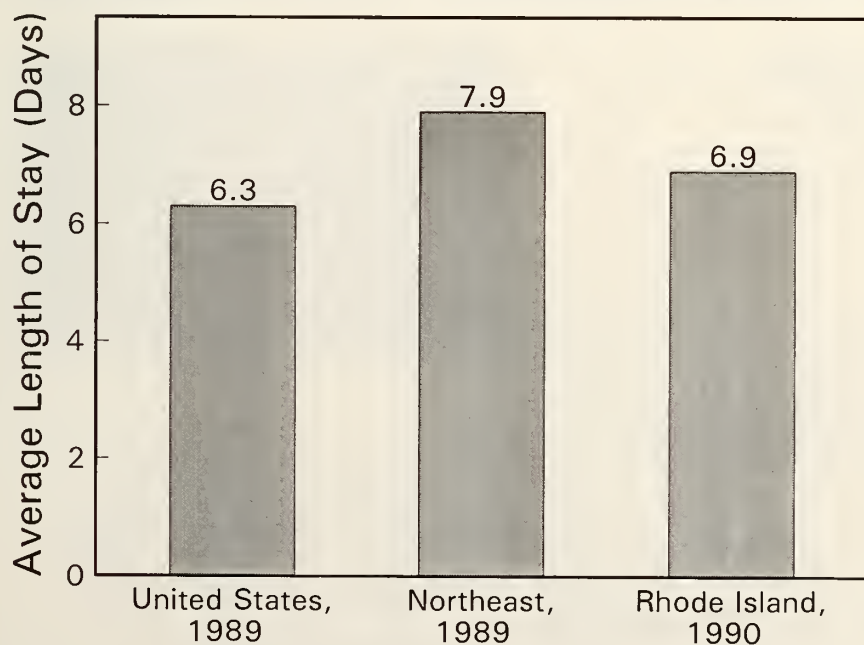
Figure 2. Rate of Hospital Discharge with Principal Diagnosis of Cholelithiasis, United States, Northeast Region, and Rhode Island, 1989-90.



The average length of stay (ALOS) for patients with principal diagnosis of cholelithiasis in Rhode Island hospitals is longer than the national ALOS for 1989 but shorter than the Northeast ALOS by a full day (Figure 3). In particular, middle-aged and elderly patients in Rhode Island experience stays that average 7% and 11% longer, respectively, than their national counterparts.

Most Rhode Island patients who are treated with cholecystectomy are discharged home, either without further care (90.7% in 1990) or with a plan for follow-up home care (3.9%). Some, primarily the elderly, are discharged to a nursing facility (2.6%) or transferred to another acute-care hospital or other facility (1.1%). Finally, a small proportion (1.5%), nearly all of whom are age 65 or older, die in the hospital.

Figure 3. Average Length of Stay for Hospital Discharges with Principal Diagnosis of Cholelithiasis, United States, Northeast Region, and Rhode Island 1989-90.



*Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania.

Source: National Center for Health Statistics, *Detailed Diagnoses and Procedures, National Hospital Discharge Survey, 1989*, Vital and Health Statistics Series 13 Number 108, September 1991.

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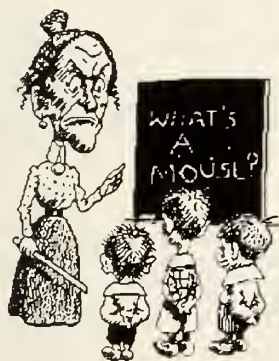
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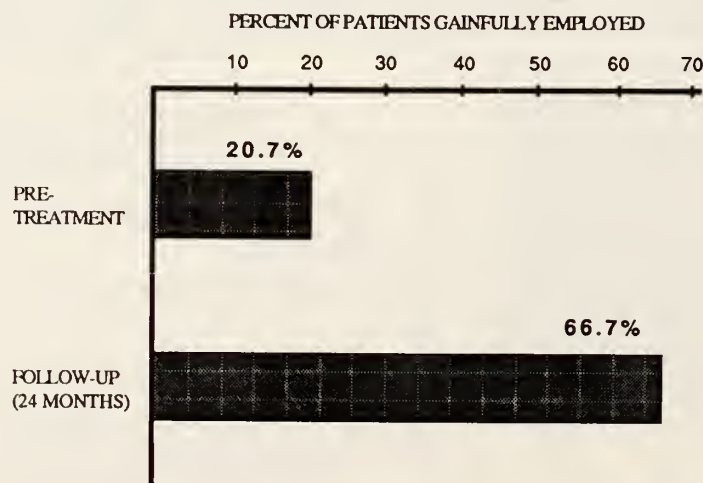
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CONTEMPORARY PROBLEMS IN MEDICINE

Doctors, Drug Companies and Gifts

Mary-Margaret Chren, MD and C. Seth Landefeld, MD

This paper by Chren and Landefeld was originally presented at the Miriam Hospital on March 21, 1991, as the 1991 Lichtman Oration, an annual meeting devoted to ethical problems in medicine honoring Herbert C. Lichtman, MD, former physician-in-chief at the hospital. Because of the importance of this paper, and its controversial character, the Journal has asked a number of practicing physicians and other concerned persons to offer their opinions on this paper. These commentaries will then be published in a subsequent issue of the Journal, along with reactions by our readers.

Companies have a right to promote their products; physicians are free to choose what to prescribe.

Being a doctor is a little like being a parent. You're totally unprepared for its all-consuming

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domination of your life, and you find its rewards beyond your most profound hopes.

But being a parent and being a doctor are different in one important way: we are not instantly given, as at the moment of our child's birth, a biologic imperative to love our patients or at least act always on their best behalf.

We must learn this mandate of our physician role. We learn it, if we're lucky as you are here at The Miriam Hospital, from our mentors and role models such as Dr Lichtman, and we learn it from our society's perception of what our role should be.

Because this role is one we assume and is not innate like parental love, we need constantly to be vigilant to situations that might threaten that role, that might cause us to act in any way other than in our patients' best interests.

We and others have been

concerned that our interactions with drug companies can represent such a situation. On the surface there is no blatant breach of conduct: companies have a right to promote their products; physicians are free to choose what to prescribe. But influences on prescribing which are independent of drug performance data may be insidious, and may represent a worrisome ethical situation. At the least, this area merits continued scrutiny by our profession.

In discussing doctors, drug companies and gifts, we will

ABBREVIATIONS USED:

ACP: American College of Physicians
AMA: American Medical Association
CME: Continuing Medical Education

describe some examples of gift interactions between doctors and drug companies, review evidence that drug promotions such as these affect physician behavior, and begin to address the difficult question of ethical ramifications by examining first three predictable but ethically neutral effects of physicians' acceptance of gifts from drug companies. There are financial consequences for patients, there may be changes in the image of the profession, and most important for us, there is the creation of a gift relationship between the physician and the company with whom he or she interacts.

Then we will discuss the rich anthropology of gifts, which are powerful regulators of human relationships. We will address three ethical repercussions of a physician's accepting a gift, including injustice, threats to the physician-patient relationships, and possible effects on our attempts to balance altruism and self interest in our professional lives. We will finish up with some practical guidelines for our behavior.

Examples of Gifts to Physicians from Drug Companies

Our friendly contact with drug companies and detail people starts as early as we learn that Eli Lilly is not a brand of stethoscope. For residents, detail people are a predictable, ever-cheerful source of friendly conversation and frequent meals. They seemed genuinely to want to develop a relationship with the house staff, asking how things were going, and always asking if they could do anything for them. While still a resident one of us began a collection of drug company gifts that came our way—we failed to predict how our interest in this topic would

lessen their interest in us (we are now never invited to meals or given gifts so this collection is rather dated).

But you know what we're talking about—social interaction between doctors and drug reps is lubricated by a steady stream of gifts that range from advertising trinkets to those of substantial value. Some are useful enough to fill those annoying voids in life—who ever has enough briefcase-sized umbrellas? Or how could we continue the business of seeing patients without the ubiquitous office paraphernalia? In case you doubt how ubiquitous, consider these 1988 data² about promotional materials in patient care areas of one practice—a family medicine training center at The Medical University of South Carolina (Table 1). As you can see, in the suite there were 5 pens, 36 note pads, 1 drug sample, 55 pamphlets and educational posters, and 43 trinkets (such as pushpins, gadgets, key rings, clocks, calendars, paper clip holders, cups, and bags)—a total of 140 pieces of promotional material. This averages out to 4.12 pieces of marketing material per individual patient-care area.

Some gifts we've received are amusingly idiotic, such as beach sandals and foot-shaped coffee mugs to remind us to treat Tinea Pedis with a certain ointment, but some are significant, such as a check for \$156 made out to one of us as a senior resident, or an invitation to stay—all expenses paid—for six nights at a posh Washington hotel, or many textbooks and journals (junior residents in Dermatology at our hospital received the three-volume set *Textbook of Dermatology* by Arthur Rook, for which the list price is \$495).

Many of the interactions in-

Table 1 Promotional Materials in Patient-Care Areas of one Practice

Pens	5
Notepads	36
Drug Samples	1
Pamphlets & Educational Posters	55
Trinkets	43
Total	140
Average per Patient Care Area	4.12

(Shaughnessy AF. JAMA 1988; 260:926)

volve food and entertainment; the residents in our departments average at least one meal per week at drug company expense. Lest you think that these affairs are a tacky Midwest phenomenon, and that you on the east coast have somewhat loftier standards, you may be interested to learn about The Second Annual New England Gallstone Biliary Symposium in Newport, sponsored by a drug company and the GI division of a prominent Boston Hospital. It was a six hour extravaganza on gallstones and their treatment, featuring a "New England Lobster Clambake". Information on this affair was forwarded to me by Dr Henry Vaillant, one of our internist colleagues in Acton, Massachusetts, who wondered if the attendees' personal interest in the topic was heightened by their own ailments following the undoubtedly cholelithogenic meal.

... the residents in our departments average at least one meal per week at drug company expense.

These gifts and other marketing efforts are expensive. Data released at last Fall's meeting of the Senate Labor and Human

Resources Committee indicated that drug company expenditures on marketing account for about 15% of their revenues (which topped \$32.4 billion in 1989), more than they spend on research and development. This translates to more than \$8000 per MD and DO per year on marketing alone, at least \$5 billion. We've been trying to conceive of how much money \$5 billion is. This annual expenditure on marketing:

- is about 2/3 of the NIH annual budget of \$8 billion.

- is about 5-10 times the annual tuition of all medical students at all medical schools in the US.

- would pay the salaries of 50,000 clinical pharmacologists at the assistant professor of medicine level. That is 400 new faculty drug experts per medical school.

Who pays this \$5 billion in advertising costs? Patients pay for the marketing of drugs. Two-thirds of visits to physicians yield a prescription, and 75% of prescriptions are paid for out-of-pocket, not by insurers. Drug prices escalated 88% between 1981 and 1988 when general price inflation was 28%.

Evidence that Gifts Influence Physicians

Why do companies spend these vast amounts of money on marketing to physicians? Companies argue that they are committed to our education and that they need to let us know about their drugs. We and most observers believe that they spend this money because they take seriously their responsibilities to their shareholders. They spend this money because it sells drugs.

But hard data that our behavior is influenced by other than drug performance are difficult

Table 2. Scientific vs Commercial Sources of Influence on Physicians' Beliefs

Physician perception and usage of cerebral vasodilators and Propoxyphene
Survey of 100 MDs

68% felt drug ads had minimal influence on prescribing

71% felt impaired cerebral blood flow is a major cause of senile dementia

32% felt cerebral vasodilators were useful

49% felt Propoxyphene was superior to aspirin

Point: drug promotions affect physician beliefs and perceptions

(Avorn J et al. Am J Med 1982; 73:4)

to gather. Elegant work on this topic has been undertaken by Jerry Avorn, of the Harvard Medical School, on scientific vs commercial sources of influence on physicians' beliefs³ (Table 2). He studied physician perception and usage of cerebral vasodilators and Propoxyphene (Darvon). Both were heavily marketed by the companies as being effective, but controlled studies had shown cerebral vasodilators to be useless and Propoxyphene to offer no advantage over over-the-counter preparations. In a survey of a random sample of 100 MDs, internists and general practitioners in the Boston area, he found that 68% felt that drug advertisements had minimal influence on their prescribing; most felt that scientific sources were the

most important determinants of their behavior. Nonetheless, 71% felt that impaired cerebral blood flow is a major cause of senile dementia, a misconception whose main source was advertisements for the cerebral vasodilators, and 32% actually felt the cerebral vasodilators were useful in managing confused geriatric patients. Forty-nine percent felt Propoxyphene was superior to aspirin for analgesia. Belief in the efficacy of cerebral vasodilators correlated significantly with belief in the superiority of Propoxyphene.

Because the commercial and academic sources of information about the drugs were diametrically opposed, the physicians' beliefs about the drugs' efficacy were then a "marker" indicating from which sources their infor-

Table 3. Self-Reports of Commercial Influences on Physicians' Prescribing Behavior

371 Faculty and Housestaff

Average 1.5 brief contacts/month with drug reps

25% of faculty, 32% of residents reported changes in practice because of drug rep contact

Predictors of Housestaff change:

Brief conversations

Faculty change: Brief or extended conversations

Free meals

(Lurie N et al. J Gen Intern Med 1990; 5:240-43)

mation came. Although the vast majority of doctors see themselves as not influenced by drug ads or detail people, this study suggested the opposite. The point is that drug promotions affect physician beliefs and perceptions.

A second study looked at self reports of commercial influences on physicians' prescribing behavior, by a group from Minnesota and Wisconsin⁴ (Table 3). In this survey, 371 faculty and house staff at 7 Midwest teaching hospitals reported an average of 1.5 brief contacts per month with drug reps. Twenty-five percent of the faculty and 32% of the residents reported changes in practice because of drug rep contact. Independent predictors of house staff change in practice were brief conversations; of faculty change in practice, brief or extended conversations and free meals.

So we've discussed the amounts of patient money spent on drug promotions in the US and reviewed the scant available empirical data about possibly worrisome influences on our behavior. But it's too broad an inductive leap to jump from this to an indictment of gifts as ethically suspect. We need to think in measured, logical steps about this difficult situation, where, as Stephen Goldfinger has said, the temptation is to avoid making ethical distinctions because they are hard to make.⁵

Effects of Drug Company Gifts

We will now simply outline predictable effects of physicians' acceptance of drug company gifts, independent of any ethical repercussions (Table 4).

First, gifts cost patients money. As we've seen, prescriptions are a major patient expense, and marketing for these prescriptions adds 5 billion dol-

lars a year to their cost. Furthermore, this expense is often passed on to patients without their consent and often without their explicit knowledge. Unlike other forms of marketing, like ads, many gifts are private and not visible to patients.

... drug company expenditures on marketing account for about 15% of their revenues ... at least \$5 billion.

Second, our acceptance of gifts from drug companies may change society's perception of our profession. American society has traditionally given us great freedom to deal with conflict of interest issues ourselves without legislation. For example, consider the conflicts inherent in our fee-for-service system of reimbursement where I advise the patient whether or not to get treated, but often, if I treat, I get more income. Such conflicts are by and large not regulated by society, but left up to the good judgment of the physician, whom society regards as having the patient's best interests at heart. This view, and in fact the faith each patient has in his or her doctor may change if people believe we accept or even solicit gifts from drug companies.

Lastly, the mere acceptance of a gift does more than cost money or hurt the reputation of the profession. All gifts establish a relationship between the donor and recipient, a relationship with vague but real obligations. It is this relationship, the gift relationship, that we think is the source of the most compelling ethical dangers in the interactions between doctors and drug companies.

Now we will relate all this to ethics by expanding a bit on gifts and the gift relationship, which

Table 4. Effects of Physicians' Acceptance of Drug Company Gifts

1. Gifts cost patients money.
2. Gifts may change society's perception of our profession.
3. Gifts establish a relationship between the donor and recipient.

has interested many anthropologists and other observers of the human condition. Hopefully then the inductive leap to ethics won't seem so vast, and we will discuss some ethical repercussions of our acceptance of drug company gifts.

The Anthropology of Gifts

Webster's Dictionary defines a gift as "something voluntarily transferred by one person to another without compensation." This definition includes the key features of the common notion of a gift: that a transfer takes place, that the transfer is voluntary, and that there is no recompense. Thus, on the surface, a gift is not an exchange and is not expected nor is it intended to have any effect beyond the transfer of something

Table 5. Marcel Mauss' Insights about the Meaning of Gifts

1. Gifts are used to initiate and maintain relationships: the gift relationship.
2. Gifts entail obligations: Grateful conduct, Grateful use, Reciprocation
3. Gifts are rarely spontaneous and often not voluntary.
4. Gifts can be dangerous.

from the donor to the recipient.

We would like to suggest that Webster's definition is too narrow, missing the essence of a gift, and that the common notion is wrong. We do not expect to convince you that our suggestion is correct; indeed quantitative data—the sort we are all more comfortable with—do not exist on this point, to our knowledge. But we do hope you will entertain this suggestion as reasonable hypothesis.

The suggestion that a gift can be more than it seems is, of course, not new. Every culture's mythology includes tales such as that of the Trojan Horse, in which a gift held the seed of destruction for the recipient. It is no accident that a German word for gift has a double meaning: gift, in our sense, and poison.

A French social anthropologist, Marcel Mauss, explored the meaning of gifts in different cultures⁶ (Table 5). He noted that gifts are used to initiate and maintain relationships—the gift relationship. Among Pygmies, for example, gifts of earthen pigments and food were used to produce a friendly feeling between the persons concerned. Lest we think this behavior is limited to other cultures and other people, let us remind you that at the Annual Meeting of the American Academy of Dermatology, the power lunch of the movers and shakers is given by a cosmetic company, a modern purveyor of earthen pigments that are still used much as they were in earlier times and by other people. While internists may be tempted to think that dermatologists are intellectual pygmies, they'd only be fooling themselves.

Mauss also observed that gifts entail obligations. The obligations of the recipient of a gift

include grateful conduct, grateful use, and reciprocation. Although we in modern society have largely lost sight of the importance of gifts as regulators of human relationships, one can think of examples from daily life of the obligations of the gift relationship. Think of the phrase "much obliged," which we use to mean "Thank you." Consider how you would feel if your offer of a gift to a spouse or friend was rejected with a "no thanks" or "sorry, I can't use it." Think about the last house staff lunch you attended where the food and drink were provided by a drug company. In our hospital, each such occasion is preceded and concluded by the ritual of our chief resident's blessing the detail person and his or her employer with our thanks.

All gifts establish a relationship between the donor and recipient, a relationship with vague but real obligations.

Mauss further observed that gifts are rarely spontaneous and often not voluntary. The air of spontaneity in the offer, "my friend, I just happen to have a little something for you" is just that, so much air—when we mean "my friend, I have thought about you long and hard. I offer this gift because of what you mean to me and in light of your likes and needs." Nor are gifts at expected times—birthdays, anniversaries, visits, and holidays—fully voluntary.

Mauss noted that gifts—rather than being spontaneous and voluntary—are often made—"to maintain a profitable alliance which it would be unwise to reject, as for instance, a partnership between fishing tribes and tribes of hunters and potters."⁶ This is still the situation today.

Consider the following statement from the American College of Physicians: "A responsible and productive alliance between the medical profession and the pharmaceutical industry is unquestionably beneficial..."⁷ For the modern industrial and academic tribes, gifts may be no more spontaneous and voluntary than for the tribes described by Mauss.

Finally, gifts can be dangerous to accept. Not only may the gift be self-destructive—as in the case of the Trojan Horse. Gifts can be more powerful than contracts, which can be fulfilled and discharged. Gifts entail obligations in a continuing relationship. A gift is not only a thing without a price; it is in fact, priceless. To accept a gift without reciprocating can be to accept another's superiority and to face one's own subordination.

The gift relationship then, is one of paradox: Gifts must be given freely, but they entail an obligation. The giver must not insist on any return, yet a response is required. Gift giving is an act of generosity; however, it also serves the self-interest of the giver. Ralph Waldo Emerson decried the negative, potentially manipulative side of gifts when he wrote, "It is not the office of a man to accept gifts. How dare you give them? We wish to be self sustained. We do not quite forgive a giver."⁸

How might we, or our institutions, respond to accepting a gift from a drug company or its representative? Almost uniformly with a grateful response, the much obliged. Outright reciprocity in the form of a gift or conscious changes in our medical practices would be unthinkable to most of us. But many might establish enduring relationships. All of us have friends who dine, travel, or play golf

with the marketing representatives of drug companies. These relationships have been applauded by many of our colleagues. For example, John Lister, the urbane London correspondent to the *New England Journal of Medicine* in the 50s and 60s wrote a piece congratulating one detail man on his clever combination of salesmanship and entertainment in sponsoring a days' golf.⁹ One can only speculate that the relationship resulting from the gift of a fellow's salary or \$50,000 in unencumbered research funds are no less enduring.

Perhaps most importantly, we may respond by granting access to our time and our minds. We might listen to a sales pitch. We might sponsor or attend an educational conference that otherwise might not have been given—a conference on a topic selected or sponsored by the drug company. We might grant or facilitate access to our students and colleagues.

Does the gift relationship affect doctors? We have summarized the few published data on this point. The observational evidence is that gift relationships are promoted at great expense by drug companies, and also forbidden. These same companies, like many for-profit concerns, generally prohibit their employees from accepting gifts from business acquaintances. These prohibitions are often most strict for purchasing agents, who determine what products their employer will buy, much as physicians determine what drugs their patients will buy. Although the professionalism and motivation of most physicians may lessen their susceptibility to gifts that influence other purchasing agents, one has to wonder whether we are really immune.

We need more data on this question of influence. But we must act ethically, as always, before all the data are in.

Ethical Effects of Drug Company Gifts

Having discussed the gift relationship in its anthropological context, we will now address its ethical implications with regard to justice, the doctor-patient relationship, and the physician's character (Table 6).

Justice entails the fair allocation of burdens and benefits. The problem is that when we accept gifts from drug companies, patients pay but doctors and, undoubtedly, drug companies benefit. As one of our British colleagues so aptly observed, often "...we are being given a meal which many of our patients could not afford but which they would appreciate much more."¹⁰

It has been argued that disclosure to our patients would make the problem of injustice go away. But one must ask, does disclosure really eliminate injustice arising from the acceptance of gifts? In principle, maybe. If the disclosure is full, if the gift is presented as simply becoming part of the doctors' fee, and if the burden and benefit are fairly allocated. But in practice however, the answer is probably not. Full disclosure is not the rule. It's tough to estimate the value of gifts associated with a single patient visit. Would we disclose to all our hypertensive patients that our office supplies were provided by the maker of Verapamil-SR, to our hypercholesterolemic patients that 8 hours of continuing medical education and a fine meal were provided by the maker of Lovastatin, and to our bronchitis patients that our Caribbean holiday was at the courtesy of the maker of a new oral Ceph-

Table 6. Ethical Implications of the Gift Relationship

1. Justice
2. The physician-patient relationship
3. The physician's character

losporin? Or would we simply say to each patient that drug companies' gifts to us add significantly to the cost of their prescriptions? Thus, full disclosure doesn't look that attractive.

So the first ethical implication is injustice.

The second ethical consideration is the physician-patient relationship. All of us and many of our patients consider this a special relationship. At the very least, our role is that of a fiduciary who should act in each patients' best interest. Once a physician-patient relationship is established, nothing other than the patient's best interests should influence our care of the patient. The implication is simple. Insofar as gifts influence a physician to prescribe a drug that is less effective or more expensive than an alternative, they threaten the physician-patient relationships. Although the extent of that threat hinges on

Table 7. Guidelines Concerning Doctors and Drug Company Gifts

1. The issue should be acknowledged
2. Obligations should be minimized
3. Disclosure
4. Education must be free from commercial influence
5. Acknowledge our responsibilities to our students

the unanswered empiric issue of influence, we think it prudent to act as though gifts have their intended effects.

The third ethical consideration is our character. Physician's characters are defined by how we respond to what Al Jonsen has described as the "profound moral paradox" in which we all live,¹¹ the constant balancing between altruistic concern for others—responding to an emergency call, sacrificing sleep or leisure to serve patient's needs—and one's innate self-interest and ambition. We all recognize this incessant tension between altruism and self-interest.

The balance is precious, however. Situations that protect our self-indulgence without considering our patients' welfare may tip the balance between self interest and altruism, thereby altering our characters. Gifts from drug companies feed our human tendencies toward self-interest. They rarely foster our concern for our patients.

Guidelines for Physicians

The prevalence of gifts, their effects, and their ethical implications suggest that guidelines are needed. Justice, our special relationship to our patients, and a proper balance between altruism and self-interest are regulative ideals, but we don't always achieve our ideals. Principles and guidelines may not only clarify uncertain situations and reduce our discomfort over the present free-for-all. Hopefully, they will promote our quest to achieve our ideals. We suggest five such guidelines (Table 7).

First, the issue should be acknowledged. In the past year, many professional organizations have made statements on this issue for the first time—The American College of Physicians,

The American College of Cardiology, and The American Medical Association, among others. But recognition of the ethical danger inherent in our accepting gifts is sometimes limited. For example, the ACP states that gifts in themselves are not the issue.⁷ In considering the influence of gifts, the ACP ignores their justice. In the future, we should recognize that gifts are the issue.

The prevalence of gifts, their effects, and their ethical implications suggest that guidelines are needed.

Second, the obligations of gifts should be minimized. This principle is at the heart of the positions of both the ACP and the AMA. The ACP position is that "gifts, hospitality, or subsidies offered to physicians by the pharmaceutical industry ought not to be accepted if acceptance might influence or appear to others to influence the objectivity of clinical judgment".⁷ The AMA position is that "gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value".¹²

According to these professional organizations, some fruit are allowed. Inexpensive education gifts such as books and modest meals are okay. The AMA also endorses gifts related to work and the ACP approves funding for trips to educational sites chosen for convenience and not pleasure.

But other fruit are forbidden—such as cash, or the winter conference in Montego Bay. We must question these lists. Are they really compatible with the principles espoused by the ACP and the AMA? When is the last time any of us saw an inexpensive medical text, and do we really believe that even a modest meal

for us benefits our patients? Is it not likely that a well conducted CME course with a topic or speakers elected by a company might "influence the objectivity of our clinical judgment"?

Moreover, the litany of acceptable fruit ignores the importance of the gift relationship itself. The key here is not the monetary value of the gift, but whether it is instrumental in fostering a personal gift relationship. We suggest that if drug company gifts are accepted at all, they should be direct contributions to physicians' education or to patient care, and they should be made explicitly in ways that void the relationship or obligation of the physician to the drug company or its representative. These contributions could be channeled through nonprofit institutions such as foundations, professional societies, or academic departments. The institution that functions as middleman has ethical responsibilities as well, of course, but the subtle threat to the individual physician's character and duty to his or her patient is minimized by avoiding a personal relationship and its attendant obligations.

Clearly the simplest solution is, just say no. It is perhaps a reflection of the magnitude of the problem that the usual response to this suggestion for our colleagues is a look stating "You must be crazy." One common response is "I could stop at any time, but the gifts are all around, they're trivial, and you don't really believe they have any influence, do you?"—a response reminiscent of a garrulous and unreformed alcoholic. A second response is "I could stop at any time, but it would cost me (my fellowship funding, uncommitted research dollars or my ability to host CME events), and you

don't really believe they have any influence, do you?"

In the immediate future, "Just Say No" is no more likely to win the battle of gifts than it is to win other wars. Any steps in this direction will require a national effort.

The first two principles are that the issue of gifts must be acknowledged and that obligations should be minimized. The third principle is that of disclosure. While potential conflicts of interest are inevitable for each of us, they are more acceptable—and at least open to discussion—if our patients and colleagues are aware of them. As we have suggested, however, disclosure is not always practical, and even disclosure does not rectify an improper action. Our British colleagues cleverly suggest that we use this criterion, "... Would you be willing to have these arrangements generally known?"¹³ We would argue that although an answer of no certainly suggests a problem, an answer of yes does not mean that an action is above ethical question. Disclosure may be necessary but not sufficient.

The fourth principle applies to the special case of Continuing Medical Education which must be free from commercial influence. The ACP, AMA, and other organizations endorse this principle but recognize that much education is underwritten by drug companies. It is widely acknowledged that influence is likely by elective support of certain topics and specific speakers. It seems strange that we physicians, with our average income in 6 figures and our dedication to staying up to date for our patients, need our educational efforts underwritten at all in the future; the most straight-forward solution would be to separate the selection of

topic, speaker, and audience from the support of education. Drug companies could make contributions of their support of education to an independent national organization.

Finally, we must acknowledge our responsibilities to our students and junior colleagues. Currently, the topic is taboo. We must begin a dialogue in our teaching and act according to our principles. We should discuss the ethical dangers inherent in relationships with drug companies and their representatives, and emphasize the importance of critical consideration of primary data and expert recommendations in the choice of drugs. At the very least, these interactions should be discussed in the same formal, problem-oriented manner in which we teach about heart failure, cirrhosis, and alcoholism. Dealing with drug marketing in the time-honored, "see one, do one, teach one" approach is not appropriate.

We conclude that as individuals, physicians should avoid accepting gifts from drug companies. Patients' money is spent unfairly. Gifts may threaten the physician-patient relationship by altering our prescribing practice. Gifts may also shift the balance between altruism and self-interest in our professional lives.

As a profession, we should structure our relationship to the drug industry according to our principles and our patients' best interests.

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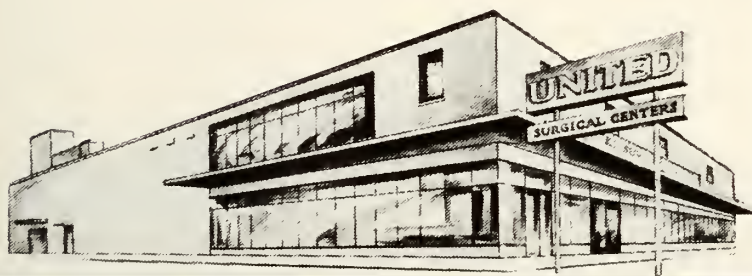
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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago (December, 1901)

George F. Keene, MD writes an article on mental enfeeblement reflecting his many years of clinical experience at the state facilities in Howard, Rhode Island. The lengthy essay begins with the following observation: "Degeneration, disease and death are but conditions of change. The individual disintegrates, the body wastes and it is the office of nutrition, growth, repair and reproduction to antagonize the processes of decay. Could the human family not only be taught but constrained to live well, then would the individual always die well and death would come as it should after fullness of years as the fruition of age." He further observes: "The nervous system stands supreme ruler of the intricate processes and functions of this mysterious organism, obedient to the manipulations and stimulus of an energizing something which we characterize as the Ego."

"The majority of State Asylum cases," he observes, "have

lapsed into an indefinite apathetic state accompanied in many instances by degenerative and trophic changes. Dementia, in their cases, is not physiological but pathological. True dementia, which is an enfeeblement or degeneration of the higher nerve centers, differs greatly from, and should not be confounded with, that stupor which is characterized by a temporary suspension of energy and is sometimes called primary dementia, acute dementia, and stuporous insanity." The author also mentions hebephrenia, dementia precox, simple diminution of mental powers, general paralysis (paretic dementia), organic dementia due to diseases of cerebral arteries, and dementia agitata as clinical subdivisions of mental enfeeblement.

Frank E. Peckham, MD offers a paper entitled "A Further Use of Hot Air." The article describes the therapeutic uses of dry heat applied to various parts of the body. He states: "The two conditions where it seems to be at its best are acute articular rheumatism and sprained

joints." He also advocates the use of dry, hot air treatment for tenosynovitis, joint dislocations, flat feet and stiff joints after fracture.

The nature of hysteria is reviewed by William McDonald, MD. The article begins with a listing of the widely varied symptoms which often accompany hysteria, including various forms and distributions of paralysis, seizures, anesthesia, abnormal sensations, behavioral changes, dementia, aphasia, and sleep disturbances. The author cites a case of a young male with hysteric aphonia treated by ether anesthesia. Immediately upon awakening the patient began to speak normally. He mentions another case of a woman with hysteric symptoms treated with bilateral nephorrhaphy, uterine curettage and oophorectomy.

The author speculates as to the nature and etiology of hysteria. "That the womb was in one way or another the seat of the disease, has formed the basis of most of the theories until comparatively recent times. Even after Sydenham and others have

combatted this theory, most authors held that it was most intimately related to sexual functions. To Charcot belongs the credit of applying for the first time, strict scientific observation to its study."

He concludes: "The animated discussions are useful, but merely because they find a certain number of conditions which are oftenest in combination and indicate how they are to be recognized. But valuable time is being lost by scientific men in useless debate which might be better spent in theorizing on the phenomena of normal life, the relation of volition to action, or on some problem which would not resemble the treading of an endless chain or the carrying to the well of a bottomless pail."

Ectopic pregnancy is considered in an article by Henry R Brown, MD after a comprehensive discussion on the usually encountered presenting signs and symptoms, and the pathologic substrate of ectopic pregnancy, the author comments on therapy. "The method of repeated injections of narcotic substances for the destruction of the fetus is more dangerous than certain, therefore to be avoided. After the sixth or seventh month the death of the fetus does not relieve the patient from the risks of an operation, for then we have the dangers of suppuration which is almost sure to follow. If you can be contented to await the event of labor pains, you will have every chance of operating and of removing a living child." And "if you have a hemorrhage get at it and apply a ligature. This rule applies equally in the case of a ruptured tubal pregnancy."

A case report of labor in dislocation of the uterus following ventrofixation and appendectomy is submitted by Herbert Terry, MD. Harry S. Flynn, MD

reports on a case of traumatic emphysema of the neck.

Fifty Years Ago (December, 1941)

The lead article, a biography of Dr Henry Turner of Newport, is written by Wilfred Pickles, MD. Turner, born in 1816, represented the fourth generation of physicians in his family. He was the eldest son of James and Catherine Turner of Warwick. His early, precollegiate training was pursued variously in East Greenwich, Portsmouth and Newport. At the age of 17 he took up the study of medicine in the office of his uncle and father and was ultimately awarded the MD degree by the University of Pennsylvania in 1836. He attempted to establish a practice in Indiana but shortly returned to Rhode Island and joined his father's office thus beginning an illustrious—and large—practice which lasted for 60 years. In addition to his enormous general practice, Turner was deeply involved in local politics (elected to the state legislature) and civic activities (president of the local Newport library). Much of his enduring fame rests upon his published observations on the treatment of head injury, particularly when associated with skull fracture. Based upon his experience in a few cases (including head injuries involving his own brother), he described procedures for cerebral decompression particularly the debridement of the depressed fracture fragments and the intentional opening of the dura mater to lower intracranial pressure. Many decades later the work of Horsley emphasized the critical importance of decompression in instances of cerebral swelling.

Ira C Nichols, MD presents a case of torula meningoencephalitis, the 96th case to be

reported in the medical literature. The patient was a 59-year-old industrial engineer. The diagnosis was established by biopsy and culture of the leptomeniges.

A case report of ovarian pregnancy is offered by Philip S. Geller, MD.

Various notices on civilian defense are evident in this month's issue of the *Journal*. There is a request for physicians to register with the Red Cross as first aid instructors. The duties of the Local Chief of Emergency Medical Services are outlined.

Amongst recently published books to be reviewed in the *Journal*: *The Treatment of Infantile Paralysis in the Acute Stage* by Sister Elizabeth Kenny, and *Technique of Contraceptive Control* by Robert L. Dickinson, MD.

Twenty-Five Years Ago (December, 1966)

Most of this issue is devoted to a symposium on sports medicine, with papers selected from various annual conferences on the medical aspects of sports sponsored by the Rhode Island Medical Society and the University of Rhode Island.

The lead article by Albert S. Hyman, MD describes technics for the estimation of cardiovascular physical fitness. The author concludes: "The need for a simple method of estimating physical fitness of the cardiovascular-pulmonary system has been recognized by physicians, physical educators and team coaches. The importance of anaerobic muscle metabolism in the production of oxygen debt has long been a study in the physiology of exercise. Insofar as a high level of physical fitness is dependent upon the ability to endure oxygen debt the factors of circulation and ventilation

assume a practical importance in all athletic activity. The investigation of these factors has and is occupying the attention of many authoritative research groups; at a high scientific level well equipped laboratory facilities and trained personnel are required to estimate functional capacity of the cardiovascular-pulmonary system in any given individual. At the moment such opportunities for sports medicine investigation are very limited in comparison with the huge number of instances where such examinations are important in the daily work of those interested in athletics and physical education in general. To this end a simple correlation formula has been discovered which employs only 7 easily obtained cardiovascular parameters. The equipment necessary has been stripped down to the ordinary working tools used for physical examination. The Cardio-Pulmonary Index at rest, after an exercise tolerance test, and after a resting period may give informative data of considerable importance. The C-P Index is not intended to substitute for scientific methods where available but on the field and in clinics where a quick and approximate determination of the cardiovascular-pulmonary system is desirable, the C-P Index is recommended."

AA Savastano, MD discusses restrictions in contact sports and lists a number of guidelines before unrestricted permission is given for participation in contact sports. He suggests that the following students should not be given permission: those lacking in any one of the paired organs; youngsters with "a tendency to be knocked out," youngsters with suspected ruptured cervical disc; recurrent dislocation of the shoulder; congenital dislocation of the hip, or youngsters with torn ligaments of the knee.

S. Turco, MD discusses the effect of sports on cardiac conditions and disparages the notion of an "Athlete's heart." He states further that the presence of a heart murmur does not necessarily denote an abnormal heart. However, cardiac lesions caused by rheumatic fever (eg, mitral stenosis) are clearly grounds for barring a student from competitive athletics. Hypertension, he states, must be verified as true organic disease and not an emotional reaction to examination before it is to be viewed as a reason to bar some-

one from competitive sports.

Further papers on eye injuries in sports, orthopedic injuries, skiing and football injuries are discussed. Additional articles on the adolescent in athletics and legal implications in athletics are presented.

Stephen J. Hoye, MD offers a paper on the current management of blunt liver trauma.

CL Hopper, MD presents a case of a 74-year-old male massive bleeding from a ruptured hepatoma apparently superimposed upon an extensive post-necrotic cirrhosis.

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A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature).

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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